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Radioiodine-125

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INTRODUCTION

Iodine-125 with half-life of sixty days is next to the longest lived among the twenty one radioactive isotopes of iodine. Its specific activity of 644 million disintegrations per second per microgram (17.4 Curies per milligram) makes it suitable as a tracer in investigations of the metabolism of stable Iodine-127.

Studies in this laboratory (1) indicate that, chiefly because of the absence of β-particles, radiation exposures will always be much less when Iodine-125 is used in place of Iodine-131 in diagnostic tracer applications. This is so notwithstanding the seven fold longer half-life. When iodide ion labeled with I^{125} instead of I^{131} is administered, at the same initial disintegration rate, the number of ergs generated in each gram of the thyroid gland will integrate to an amount of the order of one-half of the exposure, during complete decay in the gland.

The 27.4-kev X-ray and the 35.4-kev γ-ray emitted by I^{125} are efficiently absorbed by conveniently small and light detectors. These easily may be made highly directional, and they have very low background counting rates. The "broadbeam" half-thickness of the photons of about an inch in cheese (1) assures adequate penetration for most types of *in vivo* studies. A radioisotope of iodine that emits more energetic γ rays may be used for a second "uptake" or similar study by easily filtering or "tuning" out the soft I^{125} photons. The low energies of the quanta make I^{125} especially suitable for labeling compounds and substances such as iodinated serum albumin, iodinated fat, diiodosulfanilate (2, 3), et cetera, for *in vitro* assays, as well as piodophenye sulfonyl chloride (pipsyl chloride) and similar compounds for isotope derivative analyses, because of the high efficiency with which the photons are measurable.

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Obviously, providing protection against the soft Iodine-125 photons is singularly simplified.

The 60 day half-life furnishes a convenient "shelf time." It results in economy because of the greatly reduced frequencies of labeling procedures, as well as of shipping.

Autoradiographs made in cytochemical and histochemical studies by means of I^{125} should provide exceptionally high resolution because of the short ranges in cells and tissues of the Auger and internal conversion electrons.

DISCOVERY

In 1946 Reid and Keston (4) described a long-lived radioisotope of iodine which they found remaining in a solution six months after separation of radioiodine from tellurium that had been bombarded with 14.5-Mev. deuterons. It emitted radiation with absorption coefficients in copper and aluminum corresponding to the 17-kev K_a-radiation from tellurium. This indicated K-electron capture by the iodine radioisotope, which they assumed to be $Iodine^{129}$.

A few months later Glendenin and Edwards (5) gave convincing arguments for assignment of the new isotope to mass I^{125} and not to I^{129}. Friedlander and Orr (6) confirmed this assignment of the 60 day iodine to I^{125} when they demonstrated the presence of the characteristic 35.4-kev γ-ray of Te^{125} in a sample of I^{125} by means of a krypton-filled proportional counter and pulse-height analyzer.

HALF-LIFE AND DECAY SCHEME

The decay was followed for a period of seven months (6) and it was found to have a half time of 60.0 ± 0.5 days.

A decay scheme of Iodine-125 (1, 6, 7, 8, 9, 10, 11, 12) appears in Fig. 1. An attempt is made to depict in it a consensus among several of the physical findings reported in the literature that may interest the life scientist.

$Iodine^{125}$ decays solely through orbital electron capture (5) to the first excited 35.4 -kev level of Tellurium-125 according to comparisons made (6) with a sample of 58-day Te^{125m} by means of the proportional counter, as well as photon-photon coincidence measurements with scintillation counters.

The fraction of K-capture electrons was taken as 0.77 ± 0.08 and the remaining 23 per cent of the decays was presumed to occur by L_I electron capture (6). Mateosian (9) determined the L/K ratio to be 0.23 ± 0.03 by means of a scintillation spectrometer, the detector of which was a thallium-activated sodium iodide crystal grown from a melt containing I^{125} (7) so that no window corrections were required for the soft radiations and there was approximately 100 per cent efficiency. Assuming that only K and L captures occur, calculations based on this ratio give 81 per cent of the decays by capture of K electrons and 19 per cent by capture of L electrons. The rounded intermediate values chosen for Fig. 1 are those of Friedlander and Kennedy (7).

The phenomena following electron capture that are associated with the decay of the first excited state of Tellurium-125 are shown in the lower part of Fig. 1, after Bowe and Axel (12), who studied it with proportional counters in

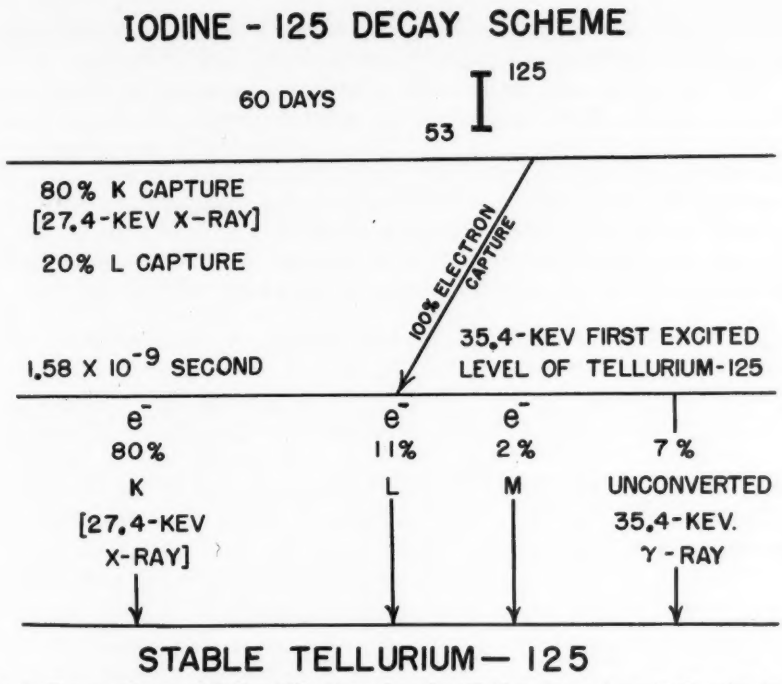

Fig. 1. Decay scheme of Iodine-125. Note that the 27.4-kev X-ray is emitted *twice* in 80 per cent of the disintegrations. The radiative yield is 0.85 so that $2 \times 80 \times 0.85 = 136 \pm 10$ of the 27.4-kev X-rays are emitted in each 100 disintegrations (Table 1).

coincidence, a NaI crystal scintillation spectrometer, and a thin lens beta-ray spectrometer.

The 35.4-kev γ-ray was found to be emitted in 7 ± 2 per cent of the decays (Table 1, Column B), in good agreement with the 7.8 per cent calculated by Friedlander, et al (13).

Hill (14) studied the energy of the γ-ray with a focusing beta-ray spectrograph and observed the L and M internal conversion electrons of the 35.4 kev γ-ray of Te^{125} photographically. Cork, et al (17) found the energy to be 35.3-kev by the same method. Bowe and Scharff-Goldhaber (11) used Geiger counters to observe the unconverted 35.4-kev photons by the characteristic fluorescence reflected from various iodine compounds.

Graham and Bell (15) found the half-life of the γ-ray transition to be $(1.58 \pm 0.15) \times 10^{-9}$ second.

Bowe and Axel (12) give the following branching values for the 35.4-kev level (Table 1, Column B): K conversion $= 0.80 \pm 0.05$; L conversion $= 0.11 \pm 0.02$; M conversion $= 0.02 \pm 0.004$ and unconverted gamma ray $= 0.07 \pm 0.02$. The K-conversion fraction had been given previously (6, 13) as 0.80 and the K/L ratio as 7.3 (15, 16). From this it follows that the tellurium characteristic K X-rays will be emitted a second time (8) in about 80 per cent of the disintegrations (Table 1, Column B). Almost all of these are 27.4-kev

K_α X-rays, although a small fraction was found (12) to be comprised of K_β X-rays that should have an energy of 31-kev.

Also associated with the process of internal conversion is the emission (Table 1, Column E) of internal conversion (I.C.) electrons with energies of 31 kev (following L conversion) and 34.3 kev (following M conversion) as reported by Bowe and Axel (12). Hill (14) had observed them previously, and Bergström (18) found them to be 30.5 and 34 kev, respectively. Since the binding energy of a K_α electron in tellurium is 31.815 kev (19, p. 78), one might also have expected 3.6-kev (35-4 − 31.8) I. C. electrons following K-capture events, but the energy was too low for them to be observed.

TABLE 1. PRINCIPAL RADIATIONS EMITTED BY IODINE–125

A Decay Process	B Percent of Decays Process Occurs	C Radiative Yield	D Percent of Decays Radiation "Emerges"	E Energy and Type of Radiation Emitted	F "Usable" Photons Emitted (% Decays)
ELECTRON CAPTURE:	100				
K Capture	80	0.855	68.4	27.4-kev K_α X-Ray	68
			11.6	22.5-kev Auger Electron	
			1.4	3.77-kev L_α X-Ray	
			10.2	2.77-kev Auger Electron	
L Capture	20	0.12	2.4	3.77-kev L_α X-Ray	
			17.6	2.77-kev Auger Electron	
UNCONVERTED GAMMA-RAY EMISSION:	7 ± 2		7 ± 2	35.4-kev γ-Ray	7
INTERNAL CONVERSION:	93				
K Conversion	80 ± 5		80	3.6-kev K I.C. Electron	
		0.855	68.4	27.4-kev K_α X-Ray	68
			11.6	22.5-kev Auger Electron	
			1.4	3.77-kev L_α X-Ray	
			10.2	2.77-kev Auger Electron	
L Conversion	11 ± 2		11	31-kev L_I I.C. Electron	
		0.12	1.3	3.77-kev L_α X-Ray	
			9.7	2.77-kev Auger Electron	
M Conversion	2 ± 0.4		2	34.3-kev M I.C. Electron	

TOTAL "USABLE" 27.4–35.4-kev PHOTONS PER 100 DISINTEGRATIONS = 143 ± 12

Not all of the X-rays that follow electron capture will "emerge" from the atom. Instead, some of them will dislodge Auger electrons from outer orbits through a process that may be thought of as an "internal" photoelectric effect. The radiative (fluorescence) yield of the 27.4-kev K_α X-rays of Te^{125} is 0.855 (19, p. 81) so that 85.5 per cent of them actually escape from the atom, as shown in Columns C, D, and F of Table 1. Thus 80 × 0.855 = 68.4 of the 27.4-kev K_α X-rays "emerge" from the atom following K-electron capture to serve as 48 per cent (68/143) of the "usable" photons that are emitted.

The 14.5 per cent that do not escape interact largely with L_I electrons with binding energy of 4.9 kev (19, p. 78) to produce Auger electrons with energy of 27.4 — 4.9 = 22.5 kev in 11.6 percent (80 × 0.145) of the decays (Table 1, Columns D and E). These were observed by Bowe and Axel (12), along with a small quantity of 25.9-kev Auger electrons that presumably followed interactions of some of the K_β X-rays with L_I electrons. The vacancy created in the L shell when the Auger electron is dislodged is filled predominantly with an electron that drops into it from the M shell; and, consequently, there is emitted a 3.77-kev L_α X-ray, as observed by Glendenin and Edwards (5). The radiative yield for tellurium L_α X-rays is about 12 per cent (19, p. 87) so that only 80 × 0.145 × 0.12 = 1.39 per cent of the decays associated with capture of K electrons is accompanied by the 3.77-kev L_α X-rays (Table 1, Columns D and E). The remaining 88 per cent of L_α X-rays produced in this part of the decay will interact largely with electrons in the M shell to produce Auger electrons with energy of 3.77 − (19, p. 78) = 2.77 kev in 80 × 0.145 × 0.88 = 10.2 per cent of the decays.

Similarly, the 20 per cent of disintegrations (Fig. 1) associated with capture of an electron from the L shell is accompanied by a 3.77-kev L_α X-ray 20 × 0.12 = 2.4 per cent of the time, and by a 2.77-kev Auger electron 20 × 0.88 = 17.6 per cent of the time (Table 1, Columns B, C, D, and E).

In the internal conversion process depicted in the lower part of Fig. 1, the events following emission of the 3.6-kev K I.C. electron are identical with those described above in the case of K capture because the frequencies are the same.

Likewise, the L-conversion radiations that follow emission of the 31-kev L I.C. electrons are identical with those given above for L capture although they occur only 11 per cent of the time, instead of in 20 per cent of the decays (Table 1).

Two per cent (12) of the 35.4-kev γ-rays (Fig. 1) eject 34.3-kev M I.C. electrons. The energy difference then appears finally in the form of very soft X-rays and Auger electrons.

PRODUCTION, AVAILABILITY, AND COST

Radioiodine-125 was discovered (4) in an old iodine sample separated from tellurium after bombardment with deuterons in the cyclotron at the Massachusetts Institute of Technology. Glendenin and Edwards (5) postulated that the I^{125} was generated in the d,2n reaction on Te^{125} and the d,n reaction on Te^{124}. They found the yield to be about 15 microcuries per microampere hour of 14 Mev deuterons, calculated on the assumption of one K X-ray per disintegration. Assuming a beam current of 50 microamperes, the yield will be about 750 microcuries per hour of bombardment. At 35 dollars per hour of bombardment time the calculated cost of generating I^{125} by this method will be about 5 cents per microcurie.

Fletcher and Amble (20) obtained one microgram of I^{125} (17,400 microcuries) in the nuclear reactions $Te^{124}(d,n)I^{125}$ and $Te^{125}(d,2n)I^{125}$ after ap-

proximately 1000 microampere hours of bombardment at the Brookhaven National Laboratory. At 40 dollars per hour of machine time for beam currents up to 50 microamperes at 20 Mev (21) the cost is again calculated to be about 5 cents per microcurie.

The Iodine-125 used in these studies during the past three years has been obtained from the Nuclear Science and Engineering Corporation at Pittsburgh, where it was generated in the same nuclear reactions by irradiation of natural elemental tellurium with 15 Mev deuterons at currents of approximately 20 microamperes (22).

A difficulty encountered when I^{125} is obtained by bombarding natural tellurium is that much larger initial quantities of 4.5-day I^{124} and 13.3-day I^{126} are generated simultaneously. The practice here has been to "age" the mixture of radioiodine isotopes for 3-4 months after it is received to "purify" it by permitting all of the I^{124} and almost all of the I^{126} to decay before experiments are begun with the I^{125} that remains in solution. Obviously this is wasteful since only 25-35 per cent of the original I^{125} activity remains for use.

Very recently (23, 24, 25) there has become available an elegant way to produce I^{125} at low cost and with insignificant contamination by I^{126}. Fourteen millicuries were generated by the $Te^{125}(p,n)I^{125}$ reaction after bombarding a 310-mg sample of 88 per cent Te^{125} as TeO_2 sealed in an aluminum capsule with 22-Mev protons for 8.3 hours. Efficient methods were evolved for separating the I^{125} and recovering the residual tellurium target that had been enriched to 88 per cent in Te^{125} from its natural abundance of 7 per cent, so that only 1 per cent of the precious ($3.5/mg) target material was lost. The estimated cost of generating I^{125}, free of other radioisotopes, based on a cyclotron operation cost of fifty dollars per hour (25) is then $8.3 \times 50 \times 100/14 \times 1000 = 3$ cents per microcurie.

Iodine-125 has also been generated in the $Sb^{123}(2n)I^{125}$ reaction by bombarding natural antimony with He^4 ions, and maximum relative yields were obtained at about 30 Mev (26). Probably around 500 microcuries of I^{125} were generated in antimony about 0.005″ thick sprayed onto an internal copper target holder after six hours of bombardment with 20-Mev A-particles at approximately 200μA (27) in the cyclotron located in Hammersmith Hospital in London (28). Based on thirty dollars an hour to operate the cyclotron (29) the cost is about 35 cents per microcurie by this reaction. Moreover, the I^{125} is contaminated initially by I^{123}, I^{124}, and I^{126}. Theoretically, the nuclear reaction $Sb^{123}(He^3,n)I^{125}$ might result in little, if any, contamination with 13.3 day I^{126} and could lead to low cost of generation when methods are evolved to prepare for bombardment, and to recover, the precious Antimony-123 that is now available enriched from its 42.75 per cent natural abundance to 96.7 per cent, at $4.40 per milligram (30).

Goeckermann and Perlman (31) obtained I^{125} "in good yield" from the products resulting from 190 Mev deuteron fission of bismuth in the 184-inch frequency modulated cyclotron at the Lawrence Radiation Laboratory at the University of California. Since absolute yields were not given, it is not possible

at this time to project "good yield" for the purposes of their study into microcurie quantities by this method of generating I^{125} in high-energy positive-ion accelerators.

Bergström described the sequence, $Xe^{125} \rightarrow I^{125} \rightarrow Te^{125}$, found in xenon after it had been irradiated in the Harwell pile (18). Subsequently he (8) irradiated 15cc of natural xenon in a quartz container for one week in a flux of 8×10^{11} neutrons/cm^2/sec and separated Xe^{125} electromagnetically and found "the e^--activity of Xe^{125} was then about 3×10^{-3} Rd, corresponding to about 0.2 mg irradiated Xe."

From this it follows that by exposure of a liter of natural xenon to 2×10^{14} n/cm^2/sec for a week one might expect to generate of the order of a Curie of I^{125}. At one hundred dollars a week for such a high neutron flux, the actual cost of generating the I^{125} could prove to be as low as about 0.01 cent per microcurie. The cost of processing should be merely that of recovery of the I^{125} from the walls of the container and scrubbing it out of the radioactive xenon after waiting about a week for the 18-hour Xe^{125} to decay into I^{125} by electron capture. Probably it would also be necessary to separate it by simple chromatographic or chemical methods from any radioisotopes of cesium that would be generated simultaneously in very small amount (32). To conserve premium space in the high-flux reactor the xenon could be compressed within an aluminum or Armco® iron container in the manner of Mann, Watson, Chrien, Zimmerman, and Schwartz (33). Similarly, yields could be greatly increased by facile enrichment of the target nuclide, Xe^{124}, from its low natural abundance of only 0.096 per cent in the thermal diffusion method of these investigators.

In his recent response to our inquiry as to the possibility of making I^{125} by this method, Schwartz (32) states, in part, ". . .production of I^{125} does not seem at all unreasonable, particularly since the thermal neutron capture cross section of Xe^{124} is fairly high: 74 b." Calculations indicate that more than ten millicuries of I^{125} will be generated in 5.9 grams of natural xenon (one liter at N.T.P.) in a week in a thermal neutron flux of 2×10^{14}/cm^2/sec for each barn of activation cross section in Xe^{124}. It is hoped that studies on the feasibility of generating I^{125} in this way might become the subject of a subsequent report from this laboratory.

Regardless of the method that will be evolved to generate I^{125} most economically, it is evident that the price need not exceed a few cents a microcurie. Therefore the cost of the Iodine-125 used in most tracer studies will be inconsequential because less than a microcurie usually will suffice, since the soft photons are absorbed efficiently by small detectors that have very low background counting rates.

ABSORPTION OF IODINE-125 PHOTONS

The emission of 136 ± 10 tellurium 27.4 kev X-rays is associated with each one hundred disintegrations of I^{125} (Table 1). "Narrow-beam" half-thicknesses of these in several absorbers were calculated (Table 2) by the relation, half-thickness $= 0.69315/\mu_m \cdot \rho$, where μ_m is the mass absorption coefficient and ρ is

TABLE 2. CALCULATED "NARROW BEAM" HALF-THICKNESSES OF 27.4-KEV PHOTONS

Absorber	Density	μ_m (cm²/g)	Cm.
Water	1.000	0.425	1.65
Al	2.717	1.44	0.177
NaI	3.667	10.2	0.0185
Cu	8.927	14.0	0.00555
Pb	11.29	40.5	0.00152

the density. Values of μ_m for 27.4-kev photons in the absorbers were obtained by graphical interpolation of those given, with coherent scattering, by McGinnies (34).

The "broad-beam" half-thickness of the 27.4-kev X-rays in distilled water was found to be 2.25 centimeters, as shown in Fig. 2. The source of I^{125} was a solution contained in a plastic bottle phantom 3.8 × 4.5 cm and 2.1 cm high that contained 27 ml, and conveniently simulated a thyroid gland (or mouse) in which the radioisotope is distributed evenly. The bottom of a thin-walled polyethylene dish 10 cm high and 17 cm diameter was centered 1.5 cm above the detector.

DETECTION, BACKGROUND, COLLIMATION, AND DIRECTIONALITY

Detectors have been especially designed (1, 35) to take advantage of the desirable physical properties of Iodine-125 (Fig. 1, Tables 1 and 2). The low energies of the X- and γ-rays result in very efficient absorption in scintillation detectors and in common metals useful for collimation and shielding.

The size of the NaI(Tl) crystal of the detector used in most of these studies is 0.25 by 1.5 inches. The copper used in the discs with holes of various diameters for the collimating system shown in Fig. 3 is ⅛ inch thick, although half this thickness should be adequate to stop almost all of the I^{125} photons. The system weighs less than a pound.

Although the crystal is about three times thicker than is necessary for efficient detection of the I^{125} quanta, the background is only 17 counts per minute when no shielding is used and a discriminator circuit (35) set to straddle the 22-38 kev energy region is interposed ahead of the scaler. When the copper collimating system is used, the background drops to 9.3 counts per minute (Table 3) or less; and, within a lead shield 1.5 inches thick, the background rate becomes about 0.7 count per minute.

The calculated "narrow-beam" half-thickness of less than 0.2 millimeter in sodium iodide (Table 2) for the 27.4-kev X-rays assures that a crystal only two millimeters thick absorbs almost all of the I^{125} photons. Consequently, the detector and collimators shown in Fig. 4 were designed. The NaI(Tl)

crystal[1] is 2 × 12.5 millimeters. It was incorporated[2] into the basic detector unit of the DS8-1 Medical Scintillation Detector Set manufactured by the Nuclear-Chicago Corporation.

Background of the unshielded detector is 5.4 counts per minute when the Nuclear-Chicago model 1810 Radiation Analyzer is set to straddle the energy region of interest. Background of this detector surrounded by one-half inch of lead is less than one count per minute. When the detector is screwed into

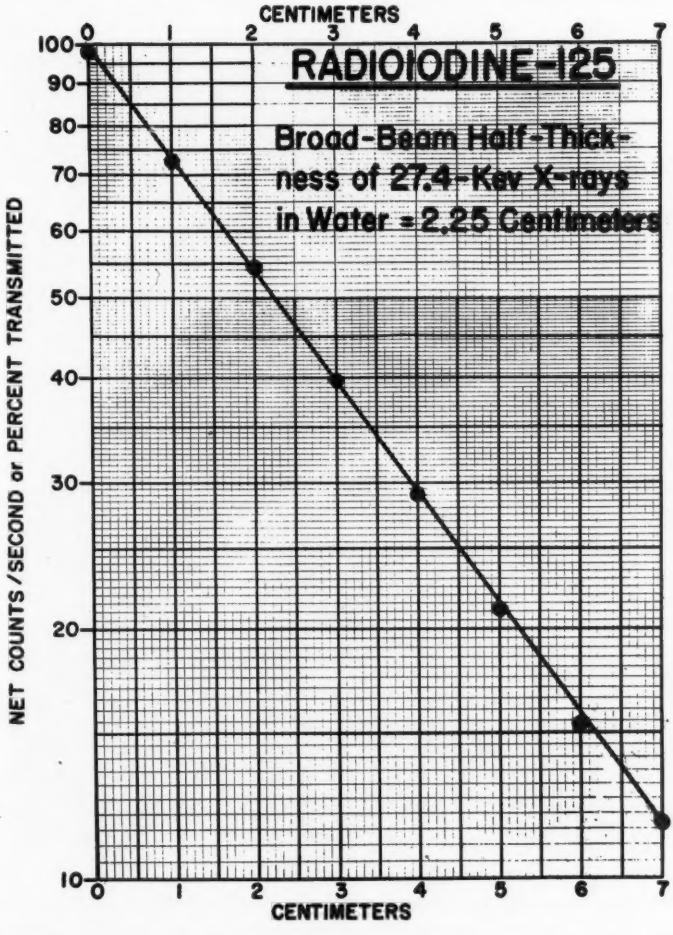

Fig. 2. Experimental "broad-beam" half-thickness of the 27.4-kev X-rays in water is 2.25 centimeters (about 0.9 inch). Percentages transmitted are: 73% through 1 cm; 54% through 2 cms; 40% through 3 cm. About 45% pass through an inch of water.

Note that about 14% is transmitted through 6.3 cm. of water. This is the calculated "narrow-beam" half-thickness of the 364-kev γ-ray emitted in 81% of the disintegrations of I^{131} (Tables 3 and 4).

the copper collimator-shield[3] with walls an inch thick the background is 2.7 counts per minute. This assembly weighs six pounds. When one of the small brass collimators shown in Fig. 4 is attached, the directional detector weighs one-half pound.

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1. Constructed by E. C. Stewart, Harshaw Chemical Company.
2. Assembled by M. E. Shepherd, Nuclear-Chicago Corporation.
3. Constructed with the kind assistance of Earl Schofield and Melvin Beidel in the shop of the Ohio State University Health Center.

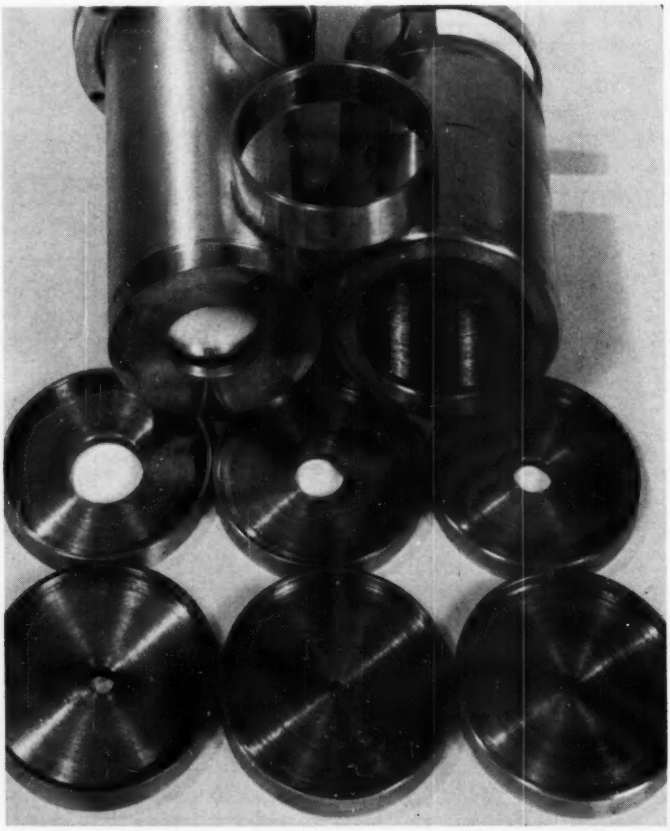

Fig. 3. The NaI(T1) crystal in the detector (upper left) used in most of these studies is 0.25 × 1.5 inch. This thickness is much more than adequate to absorb the 27.4-kev X-ray and the 35.4-kev γ-ray of Iodine-125 (Table 2). When unshielded, the background is only 17 counts per minute in the energy region of interest.

The adjustable collimator system is made of ⅛ inch copper disks with holes of various diameters and the spacer rings that go into the copper sleeve shown on the right, which is then slid over the detector. The system weighs less than a pound. Background in this system is 9.3 counts per minute (Tables 3 and 4) or less.

"Directionality" also arises inherently to an important degree when Iodine-125 is used (1) due to the fact that about half of the absorption of its 27.4-35.4 kev quanta in water occurs by the "all-or-none" photoelectric process (34, Table 27; 36, p. 12) in contrast with the absorption of high-energy photons (such as those emitted by I^{131}) predominantly by Compton scattering.

COMPARISON WITH IODINE-131.

The "narrow-beam" half-thickness in water of the 364-kev γ-ray emitted in 81 per cent of the disintegrations of I^{131} is calculated to be 6.3 cm, on the basis of interpolation of the values of absorption coefficients given by Fano (37). This half-thickness of 2.5 inches may conveniently be used to estimate the relative radiation exposures when I^{125} displaces I^{131} for labeling "photon carriers" such as diiodosulfanilate (2, 3), o-iodohippurate (38), iodinated serum albumin, et cetera, for *in vivo* dynamic studies of kidney function, myocardial blood flow (39), cardiac output, and the like, as well as for making "photon icons" of the thyroid gland, blood pools (40), and liver (41).

For I^{131}: Assume that about 200,000 electron-volts (42, p. 25) of "useless" radiation, largely in the form of shortrange β-particles, is absorbed in each disintegration; and that 81 per cent of the disintegrations are accompanied by a 364-kev γ-ray to which the detector is "tuned." Then, $100/81 = 1.24$ disintegrations are required to give one useful "signal" that will be accompanied by $1.24 \times 200{,}000 = 247{,}000$ electron-volts of useless ionizing radiation.

If one half-thickness (6.3 cm) of water be interposed between the I^{131} and the detector, then $2/0.81 = 2.47$ disintegrations will be required to furnish one "signal." This will be accompanied by $2.47 \times 200{,}000 = 494{,}000$ electron-volts of worthless and undesirable β-radiation. Also, an additional 364,000 electron-volts of useless radiation exposure will occur due to the absorption of one of the 364-kev γ-rays in the half-thickness of water. Further, the "signal" will be accompanied by $2.47\ (100 - 81) = 0.47$ useless γ-ray that falls above or below the discriminator window. Assuming for simplicity that the "average" energy of this γ-ray is about 364-kev also, and that about one-half of it is absorbed in the 6.3 cm of water, then $0.47 \times 364/2 = 85{,}000$ electron-volts of useless radiation is absorbed additionally.

The total "useless" radiation absorbed per "usable" 364 kev γ ray "signal" emitted through 6.3 cm of water is, then, $494{,}000 + 364{,}000 + 85{,}000 = 943{,}000$ electron-volts (Tables 3 and 4).

For I^{125}: To obtain "usable" 27.4-kev X-ray (Table 1), $100/136 = 0.735$ disintegration is required. It can be shown from the values in Table 1 that, when the discriminator is "tuned" to see 27.4 ± 3 kilovolts, about 16,000 electron-volts of "useless" radiation is emitted in each disintegration, largely in the form of Auger and internal conversion electrons together with a small amount of very soft X-rays and the γ-ray. Hence each 27.4-kev X-ray "signal" is accompanied by approximately $0.735 \times 16{,}000 = 12{,}000$ electron-volts of useless radiation.

If the I^{125} be located 6.3 cm beneath the surface of water, then 14 per cent (Fig. 2) will "emerge" through it, so that $100/14 = 7.14$ X-rays must start toward the detector in order that one of them can be "seen" by it. This involves

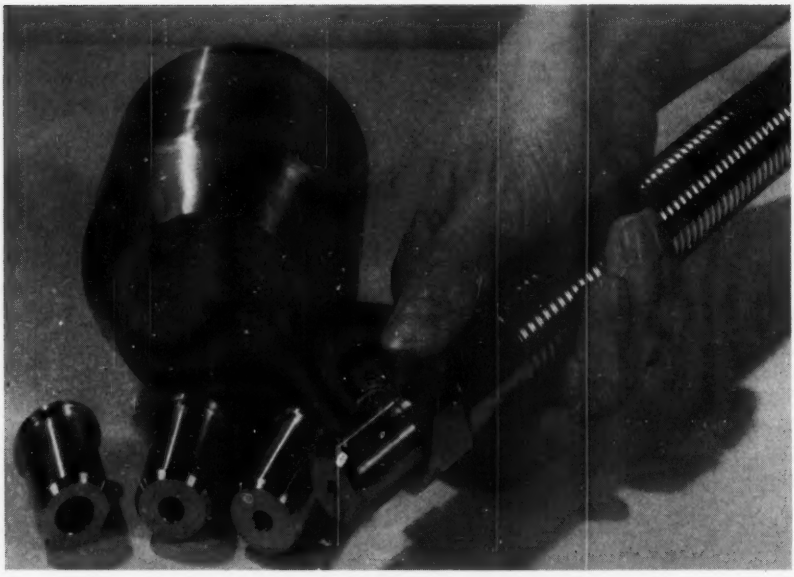

Fig. 4. The NaI(T1) crystal of this detector is 2 × 12.5 millimeters. It is incorporated into the basic detector unit of the DS8-1 Medical Scintillation Set manufactured by the Nuclear-Chicago Corp. Excellent energy resolution is achievable with this detector.

The detector and brass collimator weigh only one-half pound. Background in the energy region of interest is low, 5.4 counts per minute.

The detector can be screwed into the one inch thick copper collimator-shield shown in the upper left to reduce the background to about 2.7 counts per minute. This assembly weighs six pounds.

7.14 × 12,000 = about 86,000 electron-volts of radiation. Also, 6.14 × 27,400 = 168,000 electron-volts will be absorbed in the form of X-rays that do not reach the surface. Therefore, a total of 168,000 + 86,000 = 254,000 electron-volts of "useless" radiation will be absorbed for each usable X-ray "signal" that is emitted through the surface of the water (Tables 3 and 4).

In the interest of minimizing radiation exposures when a photon emitter is used solely as a source of signals to be detected outside of the patient, it is always desirable to maximize the photon "merit" ratio = signals/energy absorbed. And the relative merits of the two radioisotopes used for this purpose are inversely proportional to respective ratios. Hence, at 6.3 centimeters (2.5 inches) beneath the surface of the water, the relative photon merit ratio for I^{125} in comparison with I^{131} is 943,000/254,000 = 3.7.

The detector built here (1, 35) for these studies with NaI(T1) crystal 0.25 inch by 1.5 inch probably absorbs all of the I^{125} photons (Table 2) and it has a background of only 9.3 counts per minute when shielded with a few millimeters of copper. If the quantum efficiency of the crystal of the dector for 364-kev

TABLE 3. FACTORS FOR COMPARISON OF I-125 WITH I-131 FOR APPLICATIONS IN DIAGNOSIS

	Iodine–125	Iodine–131
Photon Energy	27,400 ev	364,000 ev
Photon "Signals" per 100 Disintegrations	136	81
Half-Thickness in Water	2.3 cm	6.3 cm
% Transmitted through 6.3 cm of Water	14%	50%
"Useless" Radiation Absorbed/Disintegration		
"Useless" Radiation per Photon "Signal"	16,000 ev	200,000 ev
Emitted through 6.3 cm of Water	254,000 ev	943,000 ev
Assumed Quantum Efficiency of Detector	100%	50%
Assumed Background of Detector	9.3 cpm	250 cpm

γ-rays is assumed to be 50 per cent in a background of 250 counts per minute, then advantages of I^{125} over I^{131} as a source of photon "signals" emitted from 6.3 centimeters beneath the surface of water are those summarized in Table 4.

The product of the three "merit" factors from Table 4 for I^{125} in comparison with I^{131} is about 200 under the circumstances assumed. Obviously, when the depth of the source beneath the surface is much less than 6.3 centimeters, as in the case of the thyroid gland, the relative photon merit ratio becomes much more favorable for I^{125} over I^{131}.

TABLE 4. ADVANTAGES OF 27,400-EV IODINE-125 X-RAYS OVER 364,000-EV IODINE-131 γ-RAYS EMITTED THROUGH 6.3 CENTIMETERS OF WATER[a]

1) Relative Photon "Merit" Ratio for $\frac{\text{I–125}}{\text{I–131}}$ is $\frac{\text{943,000–ev}}{\text{254,000–ev}} = 3.7$[b]

2) Quantum Efficiency "Merit" Ratio for $\frac{\text{I–125}}{\text{I–131}}$ is $\frac{100\%}{50\%} = 2.0$

3) Background "Merit" Ratio for $\frac{\text{I–125}}{\text{I–131}}$ is $\frac{250\text{ cpm}}{9.3\text{ cpm}} = 27$

4) Combined "Merit" Ratio for Iodine–125 over Iodine–131 is 3.7 x 2.0 x 27 = 200

[a] Calculated "narrow-beam" half-thickness of 364,000-ev photons in water = 6.3 centimeters (see text).

[b] When the depth of the source beneath the surface is much less than 6.3 cm, as in the case of the thyroid gland, the first "merit" ratio becomes much more favorable.

SUMMARY

Some of the principal advantages of radioiodine-125 for applications in the life sciences are summarized as follows:

1. Soft 27.4-35.4 kev X-rays and γ-rays for:

"PHOTON PROJECTION ANALYSIS"

a) Efficient detection with thin crystals
b) Background counting rates are very low
c) "Directionality" is effectively achieved
   i) Inherently "photoelectrically"
   ii) By copper, steel, lead collimators
d) Detectors are small, light, and portable
e) "Contact" teleautoradiography achievable
f) Image intensification teleautoradiography

2. **NO** β-particles; Lower radiation exposures; Soft photons; Protection is simplified
3. 60 Day half-ife; Convenient "shelf" time; Economy; Infrequent syntheses and shipping
4. High resolution autoradiography with soft Auger and internal conversion electrons

By "contact" teleautoradiography (item 1, e) is meant the recording photographically of the relative concentrations of I^{125} in a specimen in contact with the collimating system through which the photons pass to expose the emulsion on the opposite side. The sensitivity of films is near maximum for photons having the energy of those emitted by Iodine-125 (43). Studies in progress indicate this method may be useful at moderate radiation exposures. The low energy of the photons justifies efforts to study the effects of introducing small crystal intensifiers at the ends of the collimators after the method of Kellershohn and Pellerin (44). Also, activated crystal plates only 1-2 millimeters thick incorporated into Anger's scintillation camera (45, 46) might be used successfully to make "photon icons" by means of the low-energy I^{125} photons. Because image intensifiers for X-rays make possible greatly reduced radiation exposures, it is hoped to report the results of experiments now in progress to ascertain whether the pinhole principle or a collimator sytsem is the better to use with one of them for making I^{125} "teleautoradiograms" (item 1, f) of the thyroid gland and other organs.

Addendum: Since the manuscript was written, the first author has received several lots of Radioiodine-125 from the Oak Ridge National Laboratory through the kind cooperation of P. S. Baker, J. H. Gillette, and A. F. Rupp. These contained some contamination with I-126 whether the method used was the irradiation of xenon with neutrons in a reactor or the bombardment of enriched tellurium targets with protons in a cyclotron. Presumably this difficulty can be corrected as soon as obvious technical advances can be made.

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The Clinical Importance of Erythrocyte and Plasma Volume Determinations Before and After Open-Heart Surgery

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INTRODUCTION

The patient whose cardiovascular disease requires cardiotomy with extracorporeal circulation during the operation has several possible sources of abnormality in his postoperative blood volume. The disease itself is frequently associated with abnormalities of the whole blood and total red cell volumes, even before the operation. The surgical procedure and postoperative events are often associated with considerable loss of blood. Attempts at accurate replacement of lost blood are, of course, carried out during and after the surgical procedure. The replacement is usually made chiefly on the basis of continuous estimates of blood loss. Inaccuracies in the collection and measurement of the lost blood may interfere with the accuracy of the replacement. Moreover, one might a priori suspect that patients with diseases requiring cardiotomy would not be as tolerant of severe, abrupt changes in blood volume as the usual surgical patient.

A comparison of pre- and postoperative blood volumes in patients subjected to cardiotomy may thus have intrinsic interest to the physiologist and also provide useful information to guide postoperative management of the patients. Blood volume studies in patients who had undergone various procedures not involving cardiotomy or extracorporeal circulation have been reported by several authors, including Miecznikowski (1), Powers (2), and Albert (3). Kaplan (4) compared pre- and postoperative (one and two hours after operation) blood volumes in a series of patients subjected to cardiotomy with extracorporeal circulation. Kaplan measured only plasma volume directly and calculated red cell volume with the aid of the peripheral hematocrit.

In the present study the blood volumes of 17 patients before and after cardiotomy with extracorporeal circulation were compared. We determined both erythrocyte and plasma volumes directly in the majority of instances, making the postoperative determinations on the day following surgery. We have attempted to answer the following three questions. What are the size and direction of the changes in red cell and whole blood volume observed? Do the changes observed correlate in any way with the postoperative course of the patients? How do the measurements obtained by the isotope method compare with those obtained by simple collection and direct measurement of lost blood?

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TABLE 1. ANALYSIS OF VARIANCE AMONG OUTCOME GROUPS
(Optimal, Suboptimal But Survived, Died)

1a. RED CELL VOLUME CHANGE

	Determined by Isotope Method				Clinical Estimation			
	Degrees of Freedom	*Mean Square*	*F*	*p*	*Degrees of Freedom*	*Mean Square*	*F*	*p*
Among	2	1,635,765.04	4.392	$0.025 < p < 0.05$	2	4,099,556.50	6.520	$0.005 < p < 0.01$
Within	14	372,450.84			14	628,749.21		
	Means				*Means*			
	Optimal	*Suboptimal*	*Died*		*Optimal*	*Suboptimal*	*Died*	
	−437 ml	−966 ml	−1606 ml		−554 ml	−362 ml	−2294 ml	

1b. WHOLE BLOOD VOLUME CHANGE

	Determined by Isotope Method				Clinical Estimation			
	Degrees of Freedom	*Mean Square*	*F*	*p*	*Degrees of Freedom*	*Mean Square*	*F*	*p*
Among	2	3,535,091.96	5.016	$0.01 < p < 0.025$	2	42,438.89	0.202	$0.75 < p < 0.90$
Within	14	704,716.15			14	210,369.72		
	Means				*Means*			
	Optimal	*Suboptimal*	*Died*		*Optimal*	*Suboptimal*	*Died*	
	−131 ml	−1312 ml	−1575 ml		−45 ml	−204 ml	−63 ml	

MATERIAL AND METHODS

The patients studied included 10 males and 7 females. The mean age was 31 years and the range, 16 to 55 years. In most instances, cardiac catheterization had been performed as part of the diagnostic study at some time prior to operation. Six patients had an isolated interatrial septal defect. Four patients had tetralogy of Fallot (one of these had previously undergone a Blalock operation). Two patients had isolated pulmonic stenosis and one patient was operated upon for each of the following lesions: isolated interventricular septal defect, aortic stenosis, aortic insufficiency, aneurysm of the thoracic aorta, and rheumatic mitral valvulitis with insufficiency and stenosis. A left-to-right shunt was present in six patients, a right-to-left shunt present in three, and no shunt present in six. One patient had both left-to-right and right-to-left shunts and in one patient the existence of a left-to-right shunt, though probable, was not clearly established.

In one of the patients undergoing operation for tetralogy of Fallot for the first time, persistent hypotension during the operation forced abandonment of attempts to repair the lesion and the thoracotomy itself was thus the only operative procedure. In all other instances, the indicated procedure for the repair of the patient's lesion was carried out at operation. The operations were performed with the aid of an extracorporeal circulation which employed a disc oxygenator and roller pumps. Blood was collected from the venae cavae by gravity drainage and returned to the patient through the femoral artery. Body temperature was reduced to 28-30°C in most patients by means of a heat exchanger. Flow rates were adequate to maintain a mixed venous oxygen saturation of 70 per cent.

Blood loss was estimated during operation by collecting and measuring all aspirated blood and weighing the packs used. The amount of blood on the drapes was estimated by inspection. All blood introduced into the extracorporeal circulation was measured and this was balanced against the blood remaining in the circuit after perfusion. Drainage into the thoracotomy jugs following operation was measured. An attempt was made in each patient to replace all blood losses accurately. ACD solution in the citrated blood given was not considered as blood replacement. In the rough estimate of blood loss the drainage into the thoracotomy jugs following operation was considered as whole blood. Intravenous infusions of glucose and isotonic saline solutions were not considered as replacement of blood loss. A crude estimate of changes in total red cell volume was also made. As this crude estimate was based on the volume and hematocrit of all blood lost and transfused, and as the hematocrit of the blood lost was not known with certainty from moment to moment, it was necessary to make assumptions. We assumed that all loss of ≤ 6 liters represented blood with the original preoperative peripheral hematocrit, while all loss above 6 liters consisted of blood with the postoperative peripheral hematocrit. Transfused blood was assumed to have a hematocrit of 40. The above method of estimating changes in red cell and whole blood volumes will hereafter be term "Clinical Estimation" throughout the present paper.

For the accurate determination of plasma volume and total erythrocyte volume standard isotope dilution methods were employed. Plasma volume was

determined by the use of I^{131}-labeled human serum albumin and total erythrocyte volume by the use of Cr^{51}-labeling of the patients' own erythrocytes. The technique used was that described by Beierwaltes, et al. (5) with certain modifications, the most important of which were the following: erythrocytes were incubated with the Cr^{51} solution for an additional ten minutes after addition of the ascorbic acid; ten minutes after injection of the tagged erythrocytes the blood sample for determination of total red cell volume was withdrawn and the labeled albumin injected through the same needle; because of the need to avoid an excessive number of venipunctures in these patients and the need to avoid withdrawal of any sample (for counting) from the site of a previous injection of labeled material, each injection of labeled albumin was followed by withdrawal of only one sample, five minutes later. In the postoperative determination, appropriate corrections for radioactivity residual from the previous determinations were made. Although we always attempted to perform direct measurement of both red cell and plasma volumes in every instance, this was possible only in 29 of the 34 determinations reported here. In the other 5 we measured only one compartment and calculated the other from the hematocrit. In no patient was this indirect method used both pre- and postoperatively.

The postoperative course of each patient was graded by review of the entire postoperative record after discharge or death of the patient. In order to avoid possible bias the grades were given by, or confirmed by one of us who did not at the time of grading know the results of the total red cell volume changes or the isotope-determined whole blood volume changes in the patient being graded. The postoperative course was graded as "optimal", "suboptimal with survival", or death. An "optimal" course was one in which no serious postoperative complications appeared at any time and the period of postoperative discomfort was brief.

RESULTS

What are the size and direction of the changes in red cell volume and whole blood volume observed?

How do the measurements obtained by the isotope method compare with those obtained by simple collection and direct measurement of lost blood?

The answers to these questions are most conveniently given together. The mean total red cell volume was decreased postoperatively. The mean change, as determined by the radioisotope method, was —799 ml and, as calculated from "Clinical Estimation" (see above), —805 ml. The standard deviation of the differences was ±733 ml. The "t test" showed that this difference was not significant ($p > 0.8$).

The mean whole blood volume was also decreased postoperatively. The mean change, as determined by the radioisotope method, was —733 ml and, as found by "Clinical Estimation", −94 ml. The standard deviation of the differences was ±898 ml. The "t test" showed that the difference was significant ($p < 0.005$).

Do the changes observed correlate in any way with the postoperative course of the patients?

Nine patients (4 with interatrial septal defect, 2 with tetralogy of Fallot, 2 with isolated pulmonic stenosis, and one with interventricular septal defect) had

an optimal postoperative course. Five (2 with interatrial septal defect, one with aortic insufficiency, one with aortic stenosis, and one with thoracic aortic aneurysm) had a suboptimal postoperative course but survived and three (2 with tetralogy of Fallot and one with rheumatic mitral valvulitis) died. Autopsy was performed in the 3 who died. In none was there evidence of dehiscence of suture lines, major internal hemorrhage or thromboembolism, or other specific event adequate per se to cause death. A review of postoperative course and autopsy findings suggested that one patient with tetralogy of Fallot may have had an arterial channel insufficient to permit adequate outflow from the right ventricle, even after repair of the pulmonary artery. The patient who had previously undergone a Blalock procedure did poorly immediately after the more definitive repair performed here; an emergency re-exploration was therefore performed about twelve hours after the latter operation and large amounts of blood were evacuated from the mediastinum and pleural cavities. However, internal hemorrhage appeared well arrested by this last operation, and autopsy revealed no adequate cause of her death, which occurred two days following the last operation. The patient with mitral insufficiency and stenosis who died showed persistent clinical evidence of myocardial weakness throughout the postoperative period.

The mean changes in total erythrocyte and whole blood volumes and their relation to the postoperative course are summarized in Tables 1a. and 1b. There was significant correlation between postoperative course and change in total erythrocyte volume, as determined by the isotope method or calculated from "Clinical Estimation". There was significant correlation between postoperative course and changes in whole blood volume, as determined by the radioisotope method. There was no significant correlation between postoperative course and the "Clinical Estimation" of changes in whole blood volume.

Other findings.

The ratio of erythrocyte percentage in venous blood to overall erythrocyte percentage in the whole body (F_{cells} factor) (6), calculated from the preoperative values in the 16 patients who had both red cell and plasma volumes directly determined by the isotope method, was 0.91 (std. dev. ± 0.077). Although the data also suggested higher values for the F_{cells} factor in those patients with right-to-left shunts than in other patients, the number of patients in the former category was too small to permit any definite conclusion.

DISCUSSION

Studies of blood loss during gynecological (1), orthopedic (2) and other operations not requiring extracorporeal circulation have showed that blood loss is often extensive and have thus furnished good grounds for urging more complete replacement of lost blood by transfusions. The need for accurate replacement in patients undergoing cardiotomy with extracorporeal circulation is already widely accepted and the principal problems that now remain concern the best way to accomplish accurate replacement and the degree to which inaccurate replacement enhances the risk of the operation. The first and third

questions posed in the introduction concerned the changes in blood volume in patients treated by present practices and the ability of different methods to detect these changes. The combined answer to these questions (see results) is relevant to the problem of optimum replacement.

Our results suggest that whole blood volume determinations performed by the isotopic method may give one a view of the patient's situation that differs significantly from that obtained by "Clinical Estimation" of blood loss and replacement. This is not to deny the value of such "Clinical Estimation", as the latter can be carried out continuously. Furthermore, the isotope method is not immune from technical errors. Nevertheless, the desirability of checking postoperative whole blood volume changes by the isotope method seems to be supported by the fact that this method gives values that appear to correlate more closely with the postoperative course. The similarity between the mean values for total erythrocyte mass obtained by the isotope method of direct determination and the calculations based on "Clinical Estimation" is interesting. The assumptions upon which the red cell volume was calculated from "Clinical Estimation" are rough assumptions, unlikely to hold true for all patients. The wide variability in the individual differences between the erythrocyte volumes as determined by the radioisotope method and as calculated from "Clinical Estimation" in any given patient also suggests that the method of rough calculation may not be entirely trustworthy. The possibility of compensating errors must be taken into consideration. Thus, there may be a tendency for "Clinical Estimation" to underestimate whole blood loss and a tendency for the red cell loss itself to be overestimated when one assumes that the first 6 liters of blood lost have the original peripheral hematocrit (which is often very high in patients with congenital heart disease).

It seems likely that the best approach is to take advantage of the continuous availability of the "Clinical Estimation" of whole blood volume changes and to supplement this information by rough calculation of changes in erythrocyte volume based on the assumptions mentioned above. At some specified time after operation the radioisotope determination should be used. Furthermore, when the "Clinical Estimation" suggests that unusual changes are being observed or when these estimates do not coincide with the obvious clinical condition of the patient, additional blood volume determinations by the isotope method are indicated.

Certain details of the isotope method deserve further consideration. These details concern the time at which determinations are carried out, the advisability of measuring both red cell and plasma volumes directly and the use of normal standards to predict "ideal" blood volumes.

In the present study we chose the day after operation as the time at which a blood volume determination by the isotope method was likely to be most useful. Close postoperative watch of the patient's clinical condition is most likely to be carried out during the immediate postoperative hours. On the day following operation, however, many patients appear to have a stabilized condition and one must decide whether these patients are ready to be transferred to the routine of more normal postoperative care. At this point blood volume determinations by the isotope method seem logically indicated. As the patients

of the type studied here usually have their postoperative difficulties in the first few days after operation if they are going to have them at all, delay of blood volume determination until after the first postoperative day seems undesirable.

On the other hand, one may question the advisability of waiting even until the first postoperative day. In addition to the 17 patients reported here, preoperative studies were also done on 3 other patients who died during operation or in the immediate postoperative period. The fatal termination in 2 of these 3 cases was associated with hypotension starting at the time of operation and continuing till death, with lack of response to appropriate and vigorous countermeasures; it is difficult to see how information from blood volume studies at the time of the hypotension could have increased these vigorous efforts. But it cannot be denied that blood volume determinations during the immediate postoperative period might occasionally yield life-saving information. However, we determined blood volumes by the isotope method in 6 patients during the hours immediately following operation and in 4 of these the study was also repeated on the first postoperative day. Although the number of patients is too small to permit detailed comparison, the results obtained in the few hours immediately following operation appeared to be, on the whole, less helpful in predicting the patients' postoperative course than the results obtained on the first postoperative day. Of course, this may be partly due to the fact that determinations during the hours immediately following operation are likely to lead to measures to correct unusual deficiencies found then. Nevertheless, we were not surprised to find that blood volume determinations by the radioisotope method, obtained while the patient was sometimes still actively losing moderate quantities of blood and receiving transfusions, did not seem to be as reliable as those obtained on the following day.

The decision to determine both the erythrocyte volume and the plasma volume directly whenever feasible, rather than determining one and relying on the peripheral hematocrit to calculate the other, was based on the evidence that the ratio of peripheral cell percentage to whole body cell percentage is not constant. This evidence has been reviewed elsewhere (6, 7). Our results agree with those reported by previous investigators, not only in the mean value for the F_{cells} ratio in our patients but, more important, in the evidence of variability from patient to patient.

Serial determinations have the great advantage that one is not required to refer the values to some "ideal" standard. Although normal standards for blood volumes, based on weight, surface area, etc. are available, these are subject to some dispute at present. Therefore, while we do not recommend that any useful information obtained by comparing preoperative values with normal standards be disregarded, a comparison of pre- and postoperative values may give information of more immediate importance.

Although our results suggest an affirmative answer to the question regarding possible correlation between blood volume changes and clinical course, we wish to make clear that the finding of a correlation between changes in blood volume and postoperative course in no way implies that this relation is necessarily simple cause and effect. Obviously, many factors determine the postoperative course.

The correlation observed here suggests that accurate replacement of whole blood and red cell volumes is very important in decreasing mortality and morbidity and therefore deserves continuing attention. Nevertheless, in many instances other factors that influence the postoperative course may themselves secondarily influence the changes in whole blood or red cell volume. Moreover, in certain instances, a deliberate reduction in blood volume postoperatively may be advisable. For example, in one patient among the above 17, an interatrial septal defect with a left-to-right shunt was associated with a surprisingly high preoperative blood volume. The high venous pressure observed during the operation strongly suggested that the preoperative determination had indeed been accurate. Therefore, this patient was deliberately allowed to receive insufficient replacement of blood lost. Although his immediate postoperative course was suboptimal, he survived. For the purposes of statistical analysis, we have recorded the changes in blood volume without any subclassification into those deliberately allowed and those not deliberately allowed to happen. Nevertheless, we certainly do not deny that there are circumstances in which clinical judgment may indicate that the patient is better off with a postoperative blood volume that differs significantly from his preoperative blood volume. Such individual cases, however, do not contradict the facts that one is usually striving for correct replacement of blood lost and that accurate knowledge of the changes in blood volume is a sine qua non for accurate replacement.

SUMMARY

Total erythrocyte volume determined with Cr^{51}-labeled erythrocytes and whole blood volume, obtained by adding total erythrocyte volume to plasma volume, determined with I^{131}-labeled human serum albumin, were measured in 17 patients before, and on the day following open-heart surgery with extracorporeal circulation.

The mean ratio of venous erythrocyte percentage to whole body erythrocyte percentage (F_{cells} factor) was 0.91 ± 0.077 before operation.

The values for postoperative total erythrocyte volume and whole blood volume, determined by the isotope method, were compared with the values calculated from "Clinical Estimation", i.e. collection and measurement of blood lost and measurement of blood replaced.

The mean postoperative erythrocyte volume change, as determined by the isotope method was —799 ml. This did not differ significantly from the value of —805 ml. calculated from the "Clinical Estimation", although the two methods yielded values showing considerable discrepancies in individual patients. Changes in total erythrocyte volume, as obtained by either method, showed significant correlation with postoperative course.

The mean postoperative whole blood volume change, determined by the isotope method, was —733 ml. This differed significantly from the value —94 ml obtained by "Clinical Estimation". The postoperative course showed significant correlation with the changes in whole blood volume when the latter value was determined by the isotope method, but not when the value was obtained from "Clinical Estimation".

ACKNOWLEDGMENT

We thank Dr. Richard D. Remington of the Department of Public Health Statistics, University of Michigan, for his valuable advice and assistance in the statistical analysis.

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JOURNAL OF NUCLEAR MEDICINE 1:174, 1960

Measurement of Gastric Emptying Rates in the Dog With Iridium-192 Labeled Resin Suspension and External Counting

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INTRODUCTION

The purpose of this study was to develop a method for the measurement of the gastric emptying rate of the dog, particularly as affected by operative procedures. While the barium meal may be employed to demonstrate the full stomach and measure total emptying time radiographically, the barium shadow is not an accurate indication of stomach content in the interval.

A radioisotope indicator for this purpose should display the following characteristics: inexpensive, readily available fine colloidal suspension, not appreciably absorbed through the gastro-intestinal tract, with half life of several days or weeks, emitting suitable gamma radiation.

MATERIAL AND METHOD

Ir^{192} labeled colloidal resin serves the petroleum industry as a marker between multiple products being transported in a single pipe. It settles out more slowly than the finest barium meal with which it was compared. Forty-eight hours following ingestion of 300 μc in two dogs the total activity present in the blood stream measured 0.4 per cent in one and less than 0.1 per cent in the other. The physical half life is 74 days. Spectral distribution is suitable, although the presence of several high energy gamma components is not ideal (Fig. 1).

INSTRUMENTATION AND EQUIPMENT

Activity was measured with a scintillation detector having a 1½ x 1½ inch crystal shielded with 1¼ inch lead. The collimator opening measured 4.5 x 10 cm. The spectrum from an Ir^{192} source in a water phantom as measured with the 1½ inch crystal is shown in Fig. 2. It is seen that this smaller crystal is comparatively insensitive to the higher energy components. With appropriate analyzer adjustment, the instrument detects primarily the strong gamma emission at approxi-

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mately 0.3 Mev. The effectiveness of the analyzer is reduced somewhat by high energy radiation degraded into the accepted channel energy range after penetrating the shielding (Fig. 3).

A 1.2 x 30 x 40 cm lead shield was constructed with an oval window mounted to rotate about a horizontal axis to conform to the different positions of the stomach. This 50 lb. lead shield was supported by a screw jack for raising or lowering. The position of the window relative to the stomach was monitored fluoroscopically with a mobile X-ray tube and a 6 x 8 inch fluoroscopic screen arranged to slide out of the way for scintillation counter measurements. The operator was well protected from X-ray scatter by a lead rubber screen surrounding the shield and table top (Fig. 4).

ACTIVITY MEASUREMENT

Linearity of counting rate with activity was studied with the aid of a water phantom, into which was placed a balloon simulating the stomach (Fig. 5). The small bowel, simulated with Penrose drains submerged in the phantom behind the lead shield, contributed about 10 percent of the counting rate of the same amount of activity at the window. Accordingly, the corrected rate R was calculated from the relation:

$$R = R_m - 0.1\,(R_o - R_m)$$

where R_m is the measured counting rate and R_o is the initial counting rate of the full stomach.

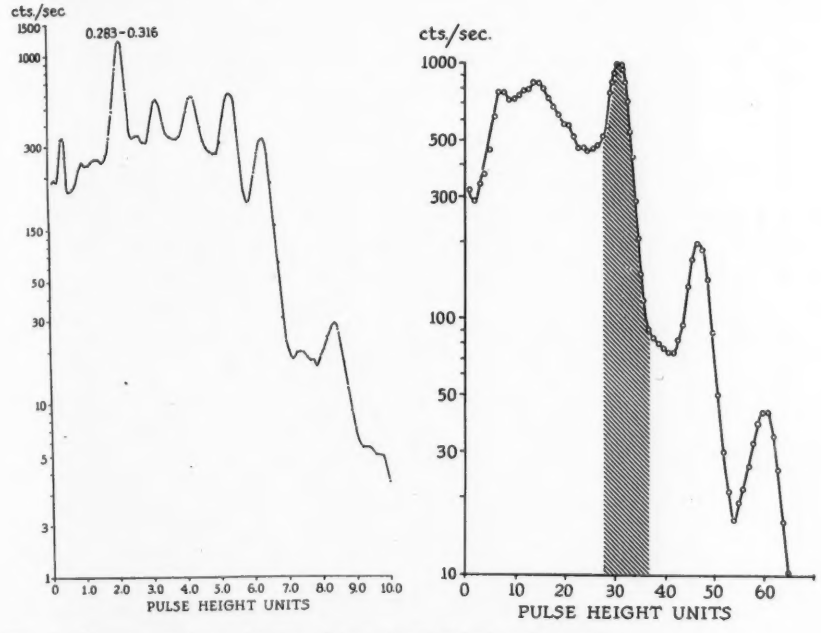

Fig. 1. Gamma spectrum of Ir^{192} as detected with 3 inch well crystal.

Fig. 2. Gamma spectrum from Ir^{192} source in water phantom detected with 1½ × 1½ inch crystal. Analyzer channel for optimum performance.

PROCEDURE

Twenty-five to thirty-five pound mongrel dogs, with Dragstedt cannulas previously affixed through the stomach wall, were immobilized in a sling behind the lead shield. The X-ray tube and scintillation counter were placed on opposite sides of the animal so that their central axes coincided and centered at the window. A 250 ml water suspension of barium sulfate and resin labeled with 300 μc Ir^{192} was rapidly injected into the stomach through the Dragstedt cannula. The stomach was immediately observed through the window fluoroscopically, and the position of the window adjusted to coincide with the barium shadow. The fluoroscopic screen was then pushed aside, and the activity recorded with the scaler, measuring of the order of 200 counts/second with the detector at 1 meter. This procedure of fluoroscopy, position adjustment, and activity recording was repeated at frequent intervals during emptying. These subsequent rates were corrected for scatter from the small bowel. Because of animal motion this method is more reliable than that of continuous recording with a ratemeter.

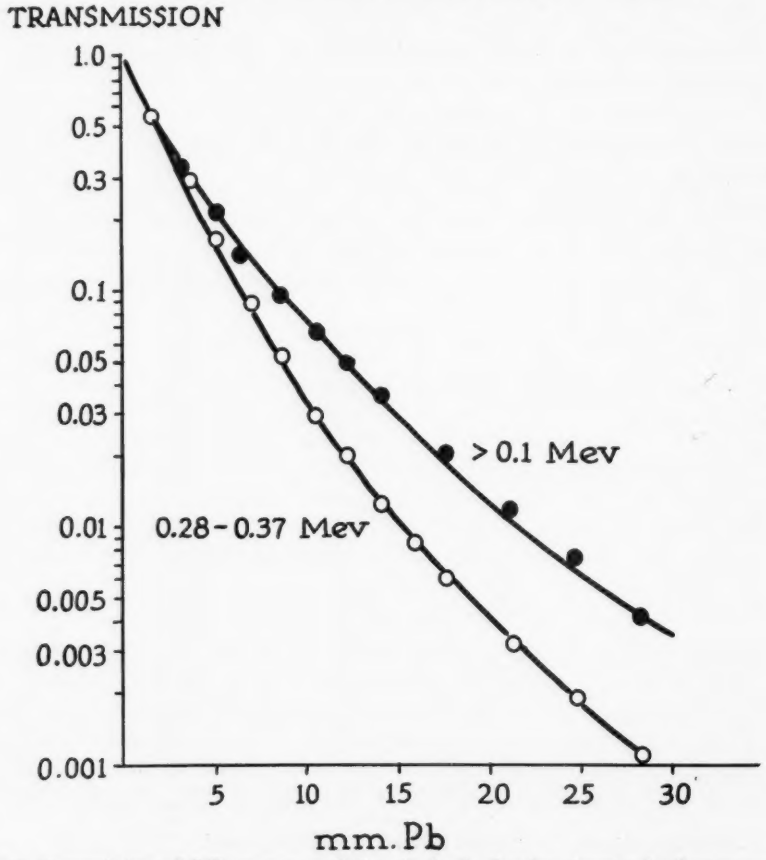

Fig. 3. Transmission of Ir^{192} gamma radiation in lead, showing improved effectiveness of shielding with the analyzer adjusted as in Fig. 2.

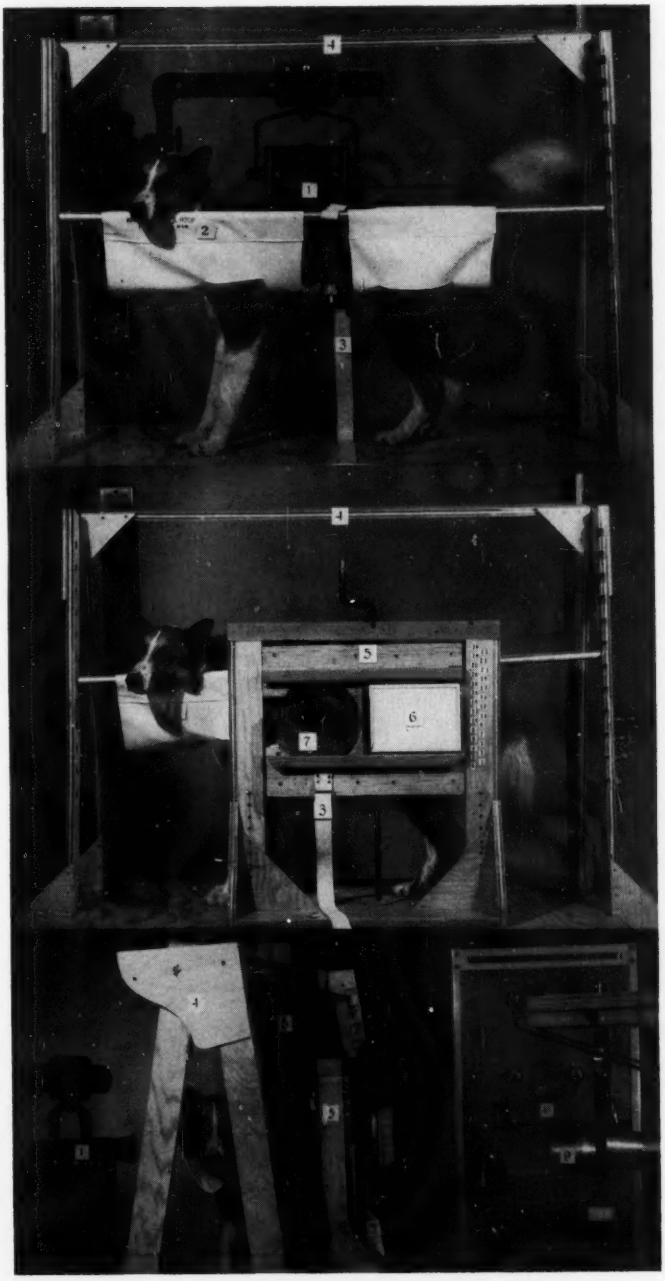

Fig. 4. (1) X-ray tube. (2), (3), (4) Immobilization. (5) Lead shield. (6) Fluoroscopic screen. (7) Window. (8) Lead rubber shield. (9) Scintillation detector and colllimator. (10) High voltage supply, pulse amplifier, analyzers, and scalers.

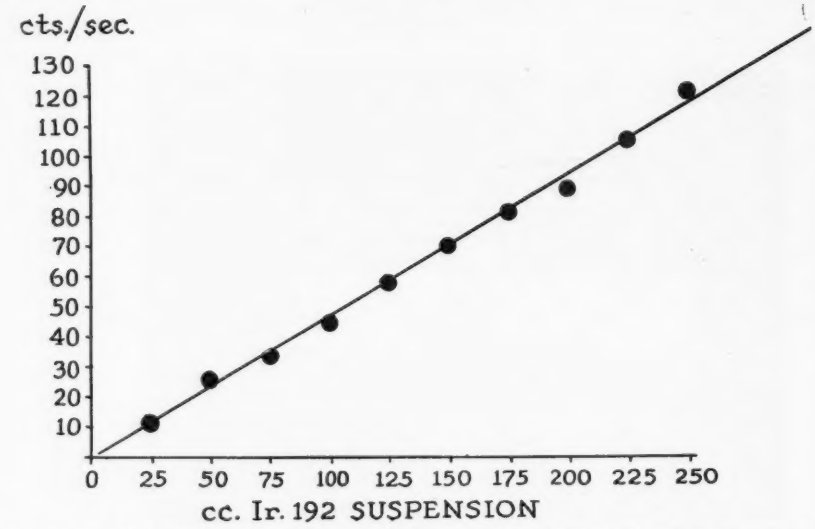

Fig. 5. Counting rate as a function of activity added to balloon, simulating stomach, in water phantom.

RESULTS

The emptying curves typical of a normal stomach together with the same stomach following two successive operative procedures are shown in Fig. 6. In this particular animal there is more rapid emptying with a small stoma than in the unoperated stomach, while following the introduction of a wide stoma, emptying is retarded. Surgical aspects of this investigation will be reported in detail elsewhere.

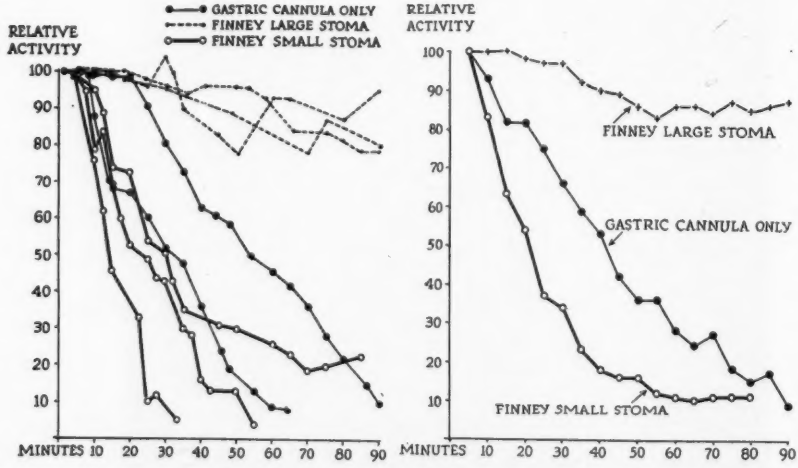

Fig. 6. a Activity measured in stomach of a dog. Multiple determination in the unoperated stomach and following two successive surgical procedures.

Fig. 6. b Average of multiple determinations shown in Fig. 6a.

DISCUSSION

In the normal stomach one loop of duodenum is visible with lateral fluoroscopic projection. However, following surgical procedures which destroy the greater omentum or alter its position, the small bowel may lie anterior or lateral to the stomach. Activity in the field from these loops may give rise to sharp brief increases in counting rate. For this reason smooth emptying curves were not always obtainable. After the stomach was essentially empty a small amount of barium could be demonstrated in the rugae. In several dogs the stomach content was removed through a second cannula installed in the duodenum. With no interfering scatter from the small bowel this residual stomach activity measured 3 per cent-10 per cent, for which no correction was considered necessary.

SUMMARY

Ir^{192} labeled resin suspension with external scintillation counting is employed in a method for the measurement of gastric emptying in the dog, especially as affected by operative procedures. Sensitivity to activity in the small bowel is reduced by extensive lead shielding, careful fluoroscopic positioning, and the use of a pulse height analyzer.

ACKNOWLEDGMENT

We gratefully acknowledge the technical assistance of Mr. Horst Drawe.

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Concentration of Labeled Tri-Iodothyronine and Radioactive Albumin in Human Cerebral Neoplasms[1]

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During the past ten years neurosurgeons have recognized the need for radioactive materials which would cross the blood-brain barrier. These substances, if concentrated within intracranial tumors, would permit accurate localization of the mass by scanning techniques and might make possible the destruction of the tumor by radiation. The major difficulty in achieving this goal is the problem of producing a material which will concentrate in the tumor after crossing the blood brain barrier.

It has been repeatedly demonstrated that cerebral tumors may be detected if sufficient amount of radioactive substance has crossed the barrier (1,2,3). The technical methods thus far developed have seemingly outstripped the search for a suitable compound which would become concentrated in cerebral tumors. Such substances should be those which cross the barrier in quantities sufficient to be easily detected by scanning techniques and be non-toxic to the recipient. Tri-iodothyronine was suggested because of its concentration in mamary adenocarcinoma of the mouse (4). Radioactive serum albumin has been used extensively in localization of cerebral tumors. This report comprises experiences with these two substances: tri-iodothyronine (I^{131}) often referred to as T3, and RISA.

METHOD

The levels of radioactivity of both T3 and RISA in cerebral tumors were studied at varying intervals following the administration of a standard dose of 500 μc of these materials. Simultaneous blood plasma measurements were obtained. Tumor tissue and normal cerebral tissue were obtained as late as 96 hours after the intravenous administration of the radioactive substances. The tumor and normal material were cleansed of blood. Representative, non-necrotic portions of each tumor having approximately equal physical sizes were then weighed and placed in a well counter. A minimum of 10,000 counts per minute was obtained in each instance. All results were referred to a standard dose and expressed in per cent of dose per gram of tissue or blood plasma.

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When RISA was used the tumor tissue was macerated and extracted with 5 percent tri-chloroacetic acid. The activity of the supernate was compared with the total. Ninety-eight to one hundred per cent of the radioactivity of the RISA was bound in the protein precipitate. At the time of this study there was no method available for tissue extraction of the T3. Chromatograms of the material received showed that the average activity due to T3 was 76-80 percent, the remaining activity was T4, Iodine, and residual fraction. The 500 μc total dose of T3 has been calculated to give 0.9 μgm/Kg in a 70 Kg human and was considered to be a tracer dose.

RESULTS

T3 was administered to 11 patients harboring cerebral tumors. No significant tumor uptake was found at the two-hour or twenty-four hour interval. There was rapid disappearance of the material in most instances from the circulating plasma, but no selective concentration in the cerebral tumors. This suggests that T3, a substance of relatively low molecular weight, merely equilibrates in a particular space. According to recent work, (5) it seems likely that the material is

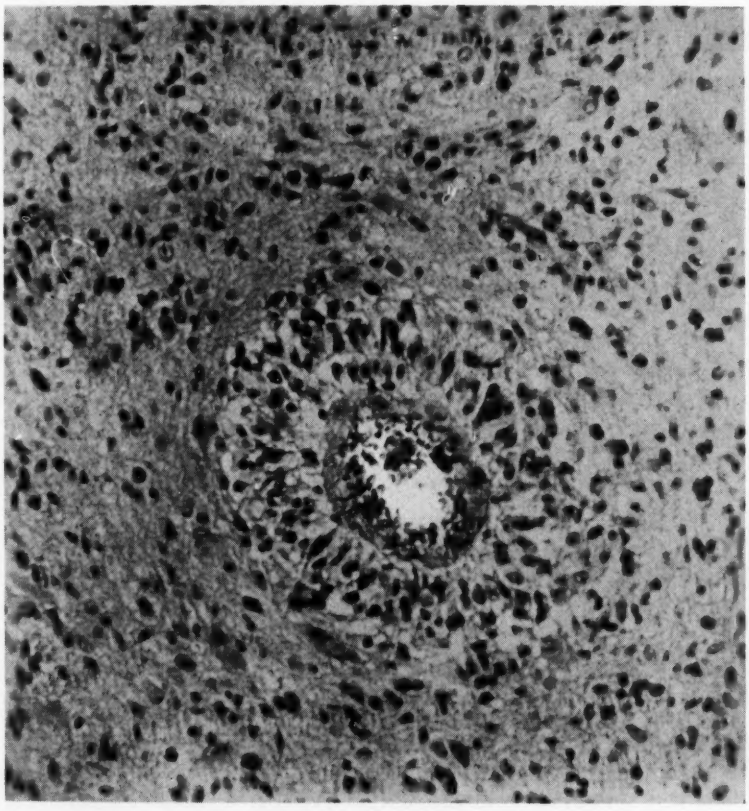

Fig. 1. An astrocytoma Grade IV. Note the tumor cells surrounding the small arteriole.

TABLE 1. UPTAKE OF I^{131} LABELED TRI-IODOTHYRONINE BY NORMAL BRAIN AND CEREBRAL TUMORS

Time After Injection	Specimen No.	Tumor Type	Tissue Uptake (% dose per gram × 10^{-3}) Plasma	Normal	Tumor
2 hr.	1	Astrocytoma Grade IV	0.50	0.63	0.31
	2	Astrocytoma Grade IV	0.43	0.37	0.28
3 hr.	3	Meningioma	1.34	0.40	0.75
	4	Metastatic Carcinoma	0.59	0.27	0.54
5 hr.	5	Metastatic Carcinoma	0.03	0.60	0.67
	6	Metastatic Carcinoma	0.02	0.21	0.33
20 hr.	7	Meningioma	0.09	0.08	0.06
24 hr.	8	Astrocytoma Grade III	0.07	0.05	0.08
	9	Hemangioblastoma	0.07	0.05	0.06
	10	Astrocytoma Grade IV	0.03	0.02	0.02
	11	Astrocytoma Grade IV	0.02	0.03	0.04

metabolized by cells of all types including the cerebrum where certain highly cellular areas maintain a positive gradient whereas the plasma level falls. From our limited data (Table I) it seems justified to note that despite the decreasing plasma levels of T3 and the maintenance of brain levels there is no overall significant concentration of T3 or its products in human cerebral tumors. Others in our laboratory are in the process of obtaining complete chromatographic data on the activity found in the tissues.

RISA was given to 21 patients. Two hours following injection there was no significant differential between the uptake of brain tumor and normal brain. At this time the blood plasma level of RISA was high. This was true of all grades of malignancy with full range in the degree of vascularity. At the 24-hour period the tumor specimens showed good differential uptake, especially the Grade IV Astrocytomas. This was not true of several of the meningiomas even though by histologic examination there appeared to be moderate vascularity. The exception to this was an angiomatous meningioma with large sinus-like channels containing the radioactive material which accounted for the substantial differential in uptake. Specimens processed at 48 hours and at 96 hours showed a tendency for an equilibrium between the counting rates of normal brain and tumor.

In table 2 the data from Specimen No. 13 are typical of a Grade IV astrocytoma in which the tumor uptake of the radioactive substance by the tumor exceeded that of the normal brain by approximately 80 per cent. If, as in this instance, there is moderate vascularity, minimal necrosis of the tumor, and no evident thrombosis of the vessels of the tumor as illustrated (Fig. 1), one must seek further answers regarding the selectivity of this material. On microscopic inspection of the smaller vessels at the presumed site of the blood brain barrier, one finds that the tumor cuffs the arterioles and the capillaries (Fig. 2). The astrocytic-capillary level is presumably the locus of the blood brain barrier which

selectively controls the passage of material between the blood and the brain. The concept of the true location of the blood brain barrier has support in the recent work of Pease, Maynard and Schulz (7), (Fig. 3). One must be careful to point out that the transfer across a barrier is selective as there is no evidence for "holes" in the capillary lap joints. The selective transfer of the T3 and RISA from the circulating blood to the brain and the tumor probably takes place at the capillary level. The boundary is permeable to the smaller molecules of T3 but is far more permeable to RISA especially in the region of the abnormal astrocytes. The transfer of RISA is molecular since one is unable to detect uncombined iorganic iodine in the tissue; namely there is no evidence to support the idea of simple ionic exchange. T3 seems to equilibrate within tumor and brain and presumably is transferred as an unaltered molecule. The validity of the latter assumption could be determined by appropriate chromatographic studies.

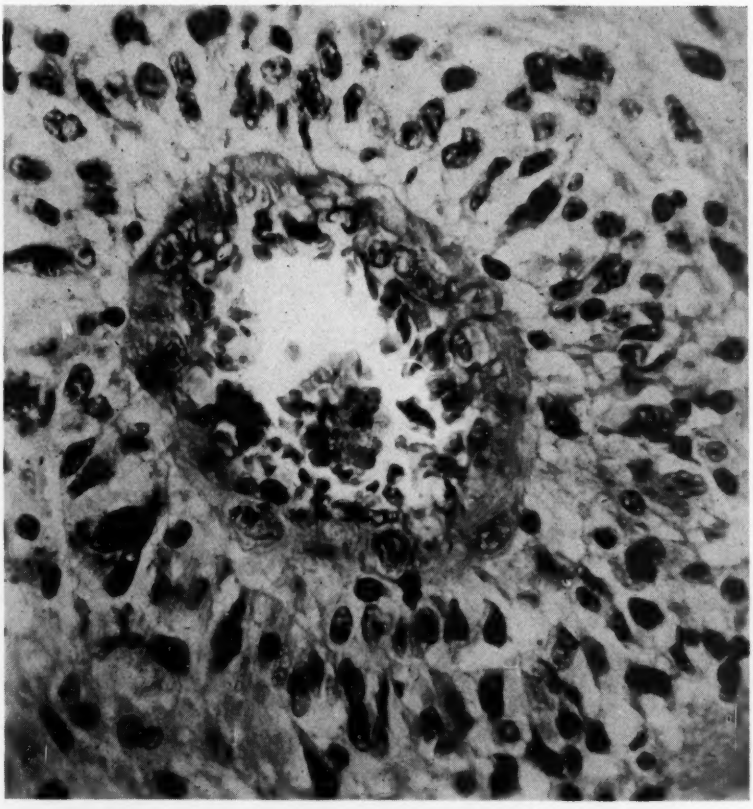

Fig. 2. A closeup of the arteriole noted in the previous figure. The vessel wall shows many swollen cells. The tumor cells have applied their feet to the vessel wall directly.

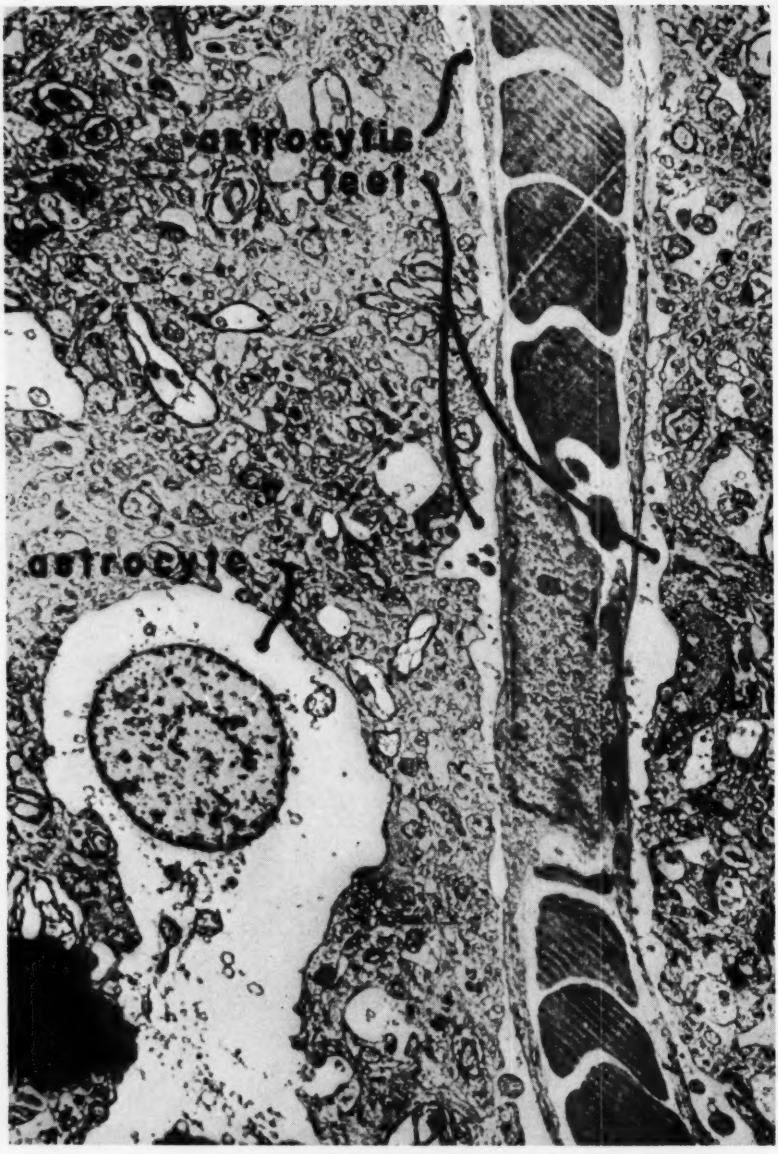

Fig. 3. An electron-microphotograph showing a cerebral capillary sectioned longitudinally. Note the sheath of watery material which are astrocytic feet surrounding the vessel wall.

"From Pease, Maynard, and Schultz in Windle, W. F., editor, BIOLOGY OF NEUROGLIA, 1958. Courtesy of *Charles C Thomas, Publisher,* Springfield, Illinois".

TABLE 2. UPTAKE OF RISA BY NORMAL BRAIN AND CEREBRAL TUMORS

Time After Injection	Specimen No.	Tumor Type	Tissue Uptake (% dose per gram × 10^{-3}) Plasma	Normal	Tumor
2 hr.	1	Astrocytoma Grade II	1.43	1.19	2.29
	2	Astrocytoma Grade III	2.53	0.77	0.06
	3	Astrocytoma Grade I	7.0	0.06	0.07
	4	Astrocytoma Grade IV	2.71	0.76	0.08
	5	Acinar Metastatic Carcinoma to bone	3.15	——	0.16
	6	Meningioma	1.52	0.18	0.52
	7	Angioblastic Epidermoid Carcinoma	1.23	0.07	0.40
	8	Dural Sarcoma	2.1	0.13	0.16
	9	Epidermoid Bronchiogenic Carcinoma	4.5	0.91	0.89
24 hr.	10	Astrocytoma Grade IV	1.24	0.05	0.24
	11	Astrocytoma Grade I	1.13	0.94	0.70
	12	Astrocytoma Grade IV	4.5	0.50	1.00
	13	Astrocytoma Grade IV	1.36	0.08	0.14
	14	Astrocytoma Grade IV	1.25	0.07	0.38
	15	Meningioma	1.4	0.50	0.66
24 hr.	16	Meningioma	1.38	0.28	0.30
	17	Astrocytoma Grade IV	1.50	0.06	0.75
44 hr.	18	Astrocytoma Grade IV	8.2	2.1	4.3
3 days	19	Metastatic Adenocarcinoma	1.9	0.7	0.38
6 days	20	Astrocytoma Grade II	1.27	0.39	0.33
13 days	21	Metastatic Bronchiogenic Carcinoma	0.73	——	0.81

SUMMARY

The data thus far collected indicate that 24 hours after the intravenous injection of 500 μc of RISA there is a significant differential between its uptake by brain tumor and normal brain, especially in the more malignant gliomas. Similar studies showed that there is not a selective uptake of tri-iodothyronine by brain tumor tissue. The problem remains of obtaining materials which preferentially cross the blood-brain barrier in a wider variety of tumors.

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JOURNAL OF NUCLEAR MEDICINE 1:186, 1960

Taurine Excretion in Humans Treated by Total-Body Radiation[1]

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INTRODUCTION

The urinary excretion of taurine (2-amino ethane sulfonic acid) has been reported to increase following total-body radiation in the rat (1, 2) and in accidentally irradiated humans (3, 4, 5). The use of total-body radiation therapy at well-defined dose levels offers a good opportunity to study this phenomenon in man. The present report consists of the preliminary results of such an investigation.

METHODS

The patients studied were hospitalized at the Naval Hospital in Bethesda because of advanced neoplastic disease. All had received previous courses of local radiation and/or chemotherapy. Total-body radiation was administered at the Naval Medical Research Institute using a cobalt-60 irradiator which can deliver an air dose at a rate of 30 r per minute in a uniform cylindrical field (6).

Twenty-four hour urine collections, as complete as possible, were obtained from each patient. Aliquots were frozen until the time of analysis. Taurine was determined by the method of Pentz (7) in which the neutral and basic amino acids of urine are removed on Dowex 50 in the acid form and the resulting filtrate is treated with Sanger's reagent to yield the dinitrophenol derivative of taurine, which is assayed photometrically. All determinations were done in duplicate. Since this method is not entirely specific for taurine (cysteic acid and tyrosine-O-sulfate, if present, would also yield color), filtrates of selected specimens from each patients were analyzed by two-dimensional paper chromatography. In each specimen tested, only a single ninhydrin-reacting spot could be detected, corresponding to taurine.

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In order to minimize errors due to incomplete collection of urine from seriously ill patients, creatinine analyses were performed utilizing the Jaffe reaction (8). Available data in the literature indicate that creatinine excretion is relatively unaffected by total-body radiation in the rat (1) and in man (4). In this report, therefore, values for taurine excretion are related to urinary creatinine.

RESULTS—CONTROL STUDIES

Among five normal adult males, each of whom contributed single-voided morning and evening urine specimens for six consecutive days, the average taurine excretion, in mg per gm creatinine, was 138 ± 52 (1 S.D.). The values ranged from 62 to 320 mg per gm, and the day to day variation in each of three subjects was greater than the variation in the entire group. There was no diurnal pattern in taurine excretion.

In a group of eight patients with cancer who had not received total-body radiation, the average daily excretion of taurine was 203 ± 70 mg per gm creatinine, and the values ranged from 50 to 326 mg per gm.

RESULTS—IRRADIATED PATIENTS

Following single acute radiation exposure given at a rate of 30 r per minute (Table 1), significant increases in taurine excretion relative to creatinine occurred in patient J. B., who was given 900 r (air dose) and in patients R. A. and J. R., each of whom received 450 r. In all three patients, levels reached a maximum on the fifth or sixth day and returned to normal between the tenth and fifteenth day post-irradiation. In contrast, patient A. B., who received the lowest dose, 225 r, showed minor changes in taurine excretion, which were not significant.

Of the four patients given multiple 100 r doses at intervals of two or three days (Table 2), patients G. A. and T. B. showed definite increases in taurine excretion beginning on the fifth day after the first dose. In the case of G. A., there appeared to be a further rise to a peak on the tenth day. Neither of these two patients experienced a marked change in clinical status during the period of study. Patients R. F. and W. H., however, exhibited more delayed responses in taurine excretion with maximal levels during the third week of therapy, when their clinical condition deteriorated.

DISCUSSION

The finding in our study of a peak in taurine excretion on the fifth or sixth day following acute radiation exposure is in agreement with the report by Kretchmar (5) that urinary taurine levels were higher on the fourth post-irradiation day than on the first day in five men accidentally exposed to mixed gamma and neutron radiation. The same author found that the changes in taurine excretion were not accompanied by a generalized amino-aciduria (4, 5).

The results in our small series of patients suggest that an increase in urinary taurine follows single total-body exposure to 450 r or greater (air dose). However, there appears to be no direct correlation between the dose of radiation and

TABLE 1

TAURINE EXCRETION FOLLOWING ACUTE TOTAL-BODY RADIATION

Pt.	*Age*	*Diagnosis*	*Total Air Dose (r)*	*Absorbed† Dose (rad)*	*5 Days Pre-Irrad. Mean ± 1 S.D.*	MG TAURINE PER GM CREATININE DAYS POST-IRRADIATION														
						1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
J.B.	35	Testic. Ca.	900	684	...	...	268	353	520	548	429	...	498	247	...	161	118	301	216	124
R.A.	36	Bronch. Ca.	450	342	161 ± 31	196	168	184	228	316	538	282	212	261	228	250	254	254	134	104
J.R.‡	7	Ac. Leuk.	450	342	232 ± 74	774	772	836	704	960	1156	958	728	586	387	405	418	372	316	285
A.B.	66	Bronch. Ca.	225	171	211 ± 109	290	350	261	247	244	288	276	...	223	193	216	237	239	222	235

Each value is the average of duplicate determinations, which varied by less than five per cent in each specimen. Underscored entries represent maximum for each patient.

†The absorbed dose, in rad, was calculated from the measured air dose, in roentgen, using a factor of 0.80 (determined in a tissue-equivalent phantom) and a factor of 0.95 to convert roentgen to rad.

‡Patient J. R. underwent multiple bone marrow aspirations under general anesthesia on the day prior to irradiation.

TABLE 2

TAURINE EXCRETION IN FOUR PATIENTS GIVEN MULTIPLE EXPOSURES

			MG TAURINE PER GM CREATININE																				
			DAYS																				
Pt.	*Age*	*Diagnosis*	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*
				†		†			†		†		†											
G.A.	11	Mesothel.		194	202	222	160	408	244	320	...	488	595	225	163	110	147	180	130	175				
				†		†		†		†														
T.B.	4	Wilms' T.	236	175	...	218	358	400	565	393	202													
				†				†		†			†		†		†							
R.F.	37	Retic. Cell Sa.		170	250	227	...	...	...	268	296	...	330	356	283	376	373	...	...	413	434	441	594	585
				†		†				†		†		†										
W.H.	59	Lymphosarc.		180	156	186	208	...	274	215	229	286	290	...	147	250	314	149	351	304				

†Indicates 100 r exposure given at beginning of specified 24-hour collection period (dose rate 30 r/min.).
... Refers to days on which urine specimens were not obtained.
___ Underscored entries represent maximum for each patient.

the amount of taurine excreted. Our group of patients is quite heterogeneous. Factors such as age, nutritional state, underlying disease processes, and renal function changes could have influenced the individual results.

The source of the taurine which is excreted in excess after radiation exposure is not known. It is hoped that further studies on patients given radiation therapy will help to elucidate the mechanisms which lead to this and other metabolic effects of irradiation in humans.

SUMMARY

1. Urinary taurine was found to increase following total-body radiation in three patients given single doses of 450 r or greater.

2. A cumulative increase in taurine excretion appeared in three other patients who received multiple 100 r doses.

ACKNOWLEDGMENT

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The Clearance of Ag^{111} From Plasma and Liver of Cirrhotic and Non-Cirrhotic Patients

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INTRODUCTION

The extremely rapid clearance of carrier free radiosilver (Ag^{111}) from the blood and liver of the rat and the extreme sensitivity of this clearance mechanism to experimentally induced liver damage has been described by Scott and Hamilton (1). The simplicity and reliability of isotopic tracer techniques makes them of great value as diagnostic aids, as in the case with I^{131} labeled Rose Bengal which has been used as a liver function test (2). We have compared the turnover of radiosilver in cirrhotic and non-cirrhotic patients in order to determine if this element might be used to measure liver function.

MATERIALS AND METHODS

Radiosilver was obtained as $AgNO_3$ from the Oak Ridge National Laboratories. This was prepared from Pd^{110} (n,γ) to form Pd^{111} which decays by Beta emission to Ag^{111}. The Ag^{111} is supplied as a carrier free solution in that no inert silver was added in the radiochemical separation of the silver from the palladium. Any inert silver in the palladium target material would be present in the Ag^{111} supplied. However, this was extremely small. It was necessary to store this material at pH 1 to keep in solution the relatively few silver atoms present, since 1 μc of Ag^{111} represents about 6.5×10^{-6} micrograms. Immediately prior to its use the pH of 10-30 μc of the Ag^{111} solution was increased to 5 with 0.1 N NaOH. The solution was then sterilized by autoclaving at 15 p.s.i. for 20 minutes and after cooling was incubated with autogenous plasma for one-half hour at 37° to form a protein silver complex.

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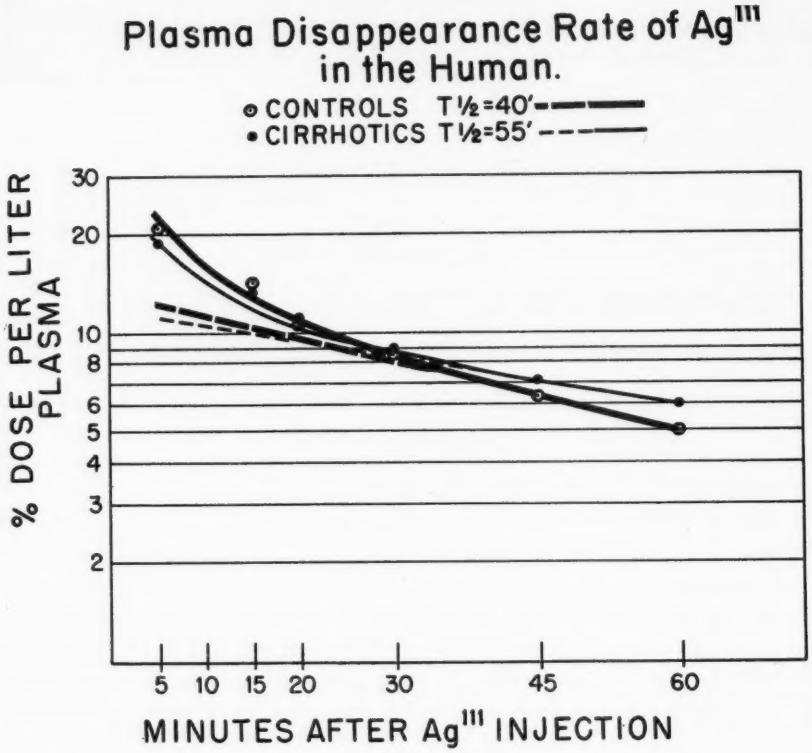

Fig. 1.

An aliquot of this preparation was taken for a standard reference and the remainder injected intravenously into the subject. The clearance of silver from the plasma was determined by using a Geiger Muller counter to assay the serial plasma samples obtained over periods of 5 to 60 minutes post injection. The distribution of radiosilver in the body was determined from autopsy specimens obtained from patients who were previously seeded with Ag^{111}. These specimens were ashed in a muffle furnace at 500° C and the ash was counted with an end window Geiger-Muller Counter. Appropriate self absorption corrections were made. The accumulation of the radiosilver in the liver was determined by external counting over the liver with a 2-inch NaI Th activated crystal recessed 1.5 inches in a straight bore collimator 3 inches in diameter.

Control subjects were selected from the medical and surgical wards of the hospital on the criteria of normal history, physical examination; and in most cases bromsulphalein, thymol turbidity, and cephalin flocculation tests for liver function were performed. The cirrhotic subjects were selected from the medical wards on the basis of cirrhosis, diagnosed by the usual clinical appraisal and laboratory tests. For purposes of comparison, the liver function of the cirrhotic patients was graded as follows: Values of 0 for normal and 1, 2, 3, and 4 for increasing severity were assigned on the basis of deviation from normal in the

Ag^{111} plasma half-time, B.S.P., cephalin flocculation and thymol turbidity tests. In comparing the various tests with the clinical status of the patient, numbers which were 66 per cent of, or closer to, each other were considered to have good correlation.

RESULTS

When the Ag^{111} plasma disappearance time was compared to the clinical appraisal of the degree of cirrhosis, 12 out of the 24 patients studied gave a 66 percent or better correlation. Similar results were obtained with B.S.P. in which 12 out of 18, or 66 percent correlated well. Five out of 11 (45 percent) and 4 out of 20 (20 percent) correlated well on the basis of the cephalin flocculation test and the thymol turbidity test, respectively.

Figure 1 is a composite graph of the average disappearance of radiosilver from the plasma of cirrhotic and control patients. After complete mixing of the radiosilver in the blood the half time in the control patients was shorter than that observed in the cirrhotic group and was 40 and 55 minutes respectively. There was considerable overlap in the half time of disappearance of silver from the plasma, ranging in the normal from 23-90 minutes and in the cirrhotics from 25-130 minutes. However, a comparison of the mean values of the percentage of Ag^{111} remaining at one hour demonstrates a significant difference between the two groups of subjects studied. (P value of .01).

Figure 2 shows the clearance of radiosilver from the liver. Following maximal uptake the half-time in the non-cirrhotic was about 11 days and in the cirrhotic 20 days. Ag^{111} assays of liver, kidney, lung, spleen, and heart, from autopsy specimens of seven terminal patients showed that the liver had by far the greatest amount and averaged 89 percent of the radiosilver administered. The approximate percentage uptake of other organs was: lung and spleen each, 4.5; kidney, 1.5; skin, 1.1; and heart, 0.5.

One subject who had received radiosilver eight days before death had 99.6 percent of the administered dose in the liver.

DISCUSSION

It is evident from the results of this study that the liver of the human handles this element qualitatively much as does the liver of the rat. There does, however, seem to be appreciable quantitative difference in this mechanism in the two species. In the rat, radiosilver was found to be quantitatively excreted in 24 hours from liver to feces. The rate of elimination in feces by the humans was markedly longer; human kidney excreted very little.

While we have demonstrated a significant difference in the rate of clearance of Ag^{111} from the plasma and liver of cirrhotic and non-cirrhotic subjects, the practicality of this procedure as a routine liver function test is doubtful. While there is statistical significance between the rates of clearance of this material from the plasma of the two groups studied, and there is good correlation of the relative time of the $t^{\frac{1}{2}}$ of clearance of silver from the plasma with the degree of cirrhosis based on medical history, the difficulty of preparing this material for use and its long period of retention in the liver are properties that may discourage its use.

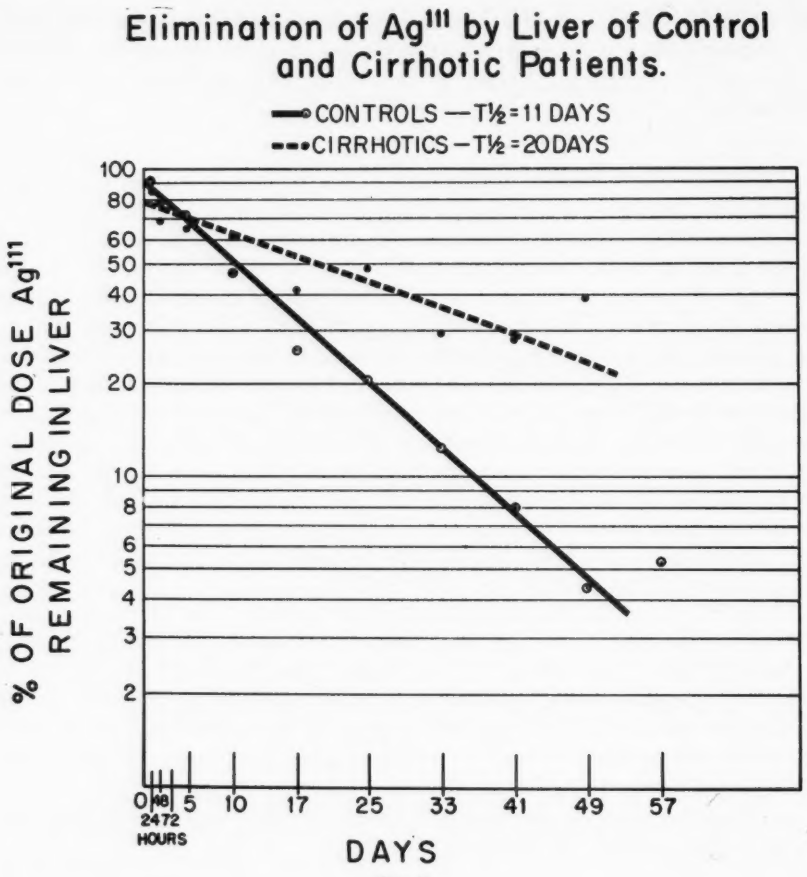

Fig. 2.

SUMMARY

The metabolism of radiosilver has been studied in the human. It has been found that radiosilver incubated with autogenous plasma and introduced into the subject by intravenous injection will be removed from the plasma principally by the liver. The rate of this removal is less in the cirrhotic subject than in the non-cirrhotic. Silver accumulated in the liver is excreted from that organ with a normal half-time value of approximately 11 days; this function is also retarded in the cirrhotic liver where the half time value is approximately 20 days.

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Summary of Ten Years of the Use of Radioactive Colloids In Intracavitary Therapy

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Intracavitary isotope therapy was pioneered by Muller in Zurich, Switzerland. He first used cyclotron-produced radioactive Zinc in 1945 and in 1950 turned to pile-produced colloidal radioactive gold, which was introduced by Sheppard, Goodell and Hahn in 1947 and made available for medical use by the Atomic Energy Commission (1).

At this time, ten years later, it seems appropriate to review the subject for evaluation of its present status and to gain a perspective for the future.

INDICATIONS

The two prime indications for intracavitary radioactive colloids are for palliative and prophylactic purposes. Palliation consists of symptomatic relief through fluid suppression. It should be reserved for those patients who are suffering from dyspnea, abdominal pressure, and deterioration due to loss of body protein from frequent taps. Pain produced by tumor invasion of sensitive structures is not likely to be helped. The malignant origin of the fluid accumulation should be reasonably well established. The general condition of the patient should be reasonably good with a survival outlook of a matter of months because it takes time for the isotope to be effective. The malignant process itself is not altered to any significant degree and the heroic use of an isotope in the terminal or cachectic patient merely brings the method into disrepute.

The prophylactic use of intracavitary isotopes to prevent local recurrence following surgery has become quite important although the use of chemotherapeutic agents for this purpose is in ascendancy. The accumulated evidence conclusively shows that malignant tumor cells are constantly being cast off into body cavities and into the circulatory system and that such shedding is precipitated or increased by surgical manipulation. Important, too, is spill from intra-abdominal cysts ruptured during removal. Some work has shown that the carcinocidal agents for "spilled" cells should be used as soon as possible after the operation (1-4).

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ISOTOPES

Colloidal gold-198 and colloidal phosphorus-32 (chromic phosphate) are both widely used for intracavitary therapy. Yttrium-90 appeared briefly on the scene but excited no widespread interest. The radiation and biological properties of Au^{198} and P^{32} have been frequently described in the literature. Colloidal gold has provided most of the information known about this form of therapy. Much of this work was done initially by Hahn and his co-workers and by the group at Oak Ridge (1, 2).

We have come to use colloidal chromic phosphate almost exclusively and feel strongly that it is the agent of choice. Although it has a larger particle size, which is theoretically disadvantageous, it has several points to recommend it:

1. Its higher beta energy, almost twice that of gold, gives greater tissue penetration but whether this makes any difference in fluid suppression is not known since the mechanism of action has not been elucidated. However, it may well be of importance in the destruction of disseminated cancer cells.

2. It has a longer half-life than gold, 14 days compared with 2.7 days. Again, whether this is more effective in suppressing fluid formation and destroying cancer cells is not proven. Certainly, shipping delays are less critical and where volume of usage justifies, the isotope can even be stocked in quantity.

3. The absence of gamma radiation is a very distinct advantage which has three important aspects:

   a. Involved personnel receive less radiation exposure.
   b. It is more economical for the patient because he does not have to be hospitalized as is the case for a gold injection.
   c. Practically no radiation sickness is produced, which is particularly important in the period immediately following surgery.

RESULTS

A summary of ten years of intracavitary therapy as revealed in the literature and through our own experience provides results from more than 50 papers (1, 2, 5, 6, 7, 8, 9). These include series of from 1 to 112 patients with results varying from 0 to 100 per cent benefit. This wide variation undoubtedly reflects the use of different criteria in selecting patients for treatment and in judging benefit. However, we feel that in total numbers there is a basis for reliable conclusions. The figures reported here include all of the treated cases in each series. Many authors prefer to exclude those patients who died too soon for any effect on fluid accumulation, but we have included them.

From the literature to date we have documented a total of 2110 patients treated palliatively with colloidal gold. Of these, 53 per cent were benefited, either by complete fluid suppression or by definite diminution in the rate of accumulation.

With chromic radioactive phosphate, 52 per cent of 222 patients have shown benefit.

These total figures include our own cases treated at Memorial Center in New York City and at St. Mark's Hospital in Salt Lake City.

Generalizing from these results of palliative therapy, we may conclude that intracavitary injection is a worthwhile procedure in slightly more than one-half of all patients. Further analysis shows very little difference between the results of intrapleural and intraperitoneal injections and it is not clear whether the primary site and histologic nature of the neoplasm are important in predicting the results of treatment. A few authors have concluded that those least likely to be helped are patients with massive tumor and adhesions, and patients that have had repeated taps over a long period of time. It is important to know that the beneficial effect appears in some patients quite promptly while in others it may not become evident for several weeks. The fact that the patient may again require tapping following isotope injection does not necessarily indicate that no benefit will be obtained.

In the prevention of local cancer recurrences by prophylactic intracavitary therapy, the first figures on end-results were published recently by Muller, who originated the method (10). He has used radioactive gold postoperatively in patients with cancer of the ovary since 1950. Fifty-one of his cases are available for a 5-year analysis. In 10 of these all gross tumor was removed and all of these are alive and well at 5 years, an unusual result for ovarian carcinoma.

Our own clinical experience with prophylactic use (1955-1958) includes 151 patients with a variety of tumors. Colloidal chromic phosphate was used in most of these patients. In only 11 of them no gross tumor was left behind and no recurrence has been demonstrated thus far in any of them. They are alive and well at 13, 14, 17, 17, 20, 22, 23, 27, 31, 34, and 36 months respectively. This group includes 7 patients with ovarian carcinoma, in 3 of which cyst rupture and spillage occurred within the peritoneal cavity.

CHEMOTHERAPEUTIC AGENTS IN INTRACAVITARY THERAPY

Nitrogen mustard and newer, related compounds are now in widespread use for this form of therapy. The first such use of a modern chemotherapeutic drug was reported by Karnofsky in 1948 (11). His observations went unnoticed until the use of radioactive colloids became popular and then it was taken up again (12, 13). Nitrogen mustard has obvious, practical advantages because it:

1. costs less than radioisotopes,
2. does not decay and so is available from the shelf at any time,
3. presents no radiation safety problem,
4. does not require a special license, and
5. can be used anywhere inasmuch as no special equipment or large hospital center is necessary.

Chemotherapeutic agents however also have some serious disadvantages. The action is by far not as well localized as with radiocolloids, as evidenced by the bone marrow depression, nausea, vomiting, and other side reactions. Fatalities have occurred within a few hours after the use of nitrogen mustard in the

pleura, which we feel is due to the severe local reaction produced by the injected drug. Theoretically, the more superficial action of the chemotherapeutic agents compared with the radiocolloids also must be considered as a drawback. We feel therefore that at the present stage, radiocolloids are preferable because they are safer and because their effectiveness is better documented.

SUMMARY

Ten years of the use of radioactive colloids for intracavitary therapy has provided the following observations:

1. In slightly more than 50 per cent of the cases, worthwhile fluid suppression is accomplished in malignant effusion.
2. The prophylactic use of radiocolloids immediately after the operation appears promising.
3. Colloidal chromic phosphate appears as the radioisotope of choice.
4. The use of chemotherapeutic agents cannot be considered at present to be as safe and as effective as the use of radiocolloids.

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Total Exchangeable Potassium Determination in Saliva Using K^{42} and RB^{86}*.

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Total exchangeable potassium is the term used to indicate the amount of total body potassium which will exchange with its radioactive isotope K^{42}. It comprises approximately 85 per cent of total body potassium. Exchange of a tracer dose of K^{42} with stable potassium (K^{39}) is usually complete within 24 hours after administration of the radioactive isotope.

Urine has been shown to be representative of an intracellar compartment insofar as potassium exchange is concerned (4); it is used for the determination of total exchangeable potassium. This is based on the dilution principle: the amount of the tracer in the body (the administered tracer dose of K^{42} less the amount excreted in the urine) is divided by the ratio of radioactive K^{42} to stable K^{39} after exchange has taken place (24 hours). This ratio is called the "specific activity".

Normal values obtained by a number of investigators are about 3500 milliequivalents for males and 2400 milliequivalents for females. A distinct difference exists between age groups (1, 2, 5) (Table 1).

It is often impossible to obtain urine from patients suffering from renal failure and consequently total exchangeable potassium cannot be measured.

Saliva, which is rich in potassium and readily available, was used to determine its applicability as a substitute for urine in total exchangeable potassium studies.

MATERIALS AND METHOD:

1. K^{42}

Radioactive potassium (K^{42}), physical half-life 12.4 hours, specific activity 0.144-0.42 mc/mg, was obtained as sterile potassium chloride from Abbott Laboratories, Oak Ridge, Tennessee. Tracer doses of 300 microcuries were made up in tap water and administered orally to eight subjects. All urine was collected for a period of 24 hours, measured, and its radioactivity determined in a deep well scintillation counter. This is the amount of K^{42} excreted. Twenty-five hour and 26 hour "spot" samples were collected and treated similarly. These are the "equilibrium" urines in which the specific activity should be constant indicating that exchange is complete.

Salivas were collected at the same hours as the urine specimens. In order to collect the salivas the patient was asked to chew a small piece of canning wax for at least two minutes. Thereafter, he continued chewing and spitting,

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*Supported in part by a grant from Abbott Laboratories, North Chicago, Illinois.

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TABLE 1.

TOTAL EXCHANGEABLE POTASSIUM (Ke)

$$\frac{K^{42}\text{ Administered} - K^{42}\text{ Excreted}}{K^{42}\text{ Urine}/K^{39}\text{ Urine}}$$

MALES	3500 Meq			
	Age	18–33	34–50	51–75
	Meq/Kg	49	45	39
FEMALES	2400 Meq			
	Age	16–33	34–81	
	Meq/Kg	37	31	

avoiding specifically coughing up sputum, until a suitable volume for counting was obtained (5 ml). The radioactivity was approximately ⅓ of the spot urine aliquots. The salivas were collected in glass jars and were easily pipetted for counting.

K^{39} was determined on all salivas and urines using a Perkin-Elmer propane flame photometer with a lithium internal standard. Appropriate dilutions were made so that readings would fall within the range of a standard curve.

RESULTS:

From the results obtained, as shown in Table 2, it is apparent that the specific activity and consequently the total exchangeable potassiums (K_e) calculated from urine and saliva show very close correlation.

TABLE 2.

SPECIFIC ACTIVITY AND KE OF URINE AND SALIVA USING POTASSIUM 42

	Specific Activity $\frac{K^{42}\ \mu c/L}{K^{39}\ Meq/L}$		Ke Urine		Ke Saliva	
	Urine	Saliva	Meq	Meq/Kg	Meq	Meq/Kg
1. (f) Control	.154	.150	1800	28.3	1900	29.9
2. (f) Diabetes	.127	.124	2270	28.2	2320	28.8
3. (m) Diabetes	.130	.120	2210	30.1	2390	32.6
4. (f) Diabetes	.193	.189	1520	30.8	1550	31.4
5. (f) Diabetes	.130	.127	2210	38.2	2270	39.1
6. (m) Heart Failure	.142	.140	2490	36.1	2514	36.4
7. (f) Diss. L.E.	.163	.159	1760	33.6	1800	34.3
8. (f) Diss. L.E.	.203	.224	1390	26.6	1260	24.1

(f) = Female, (m) = Male.

2. Rb^{86}

Rubidium has been shown to enter into the metabolic pool of potassium in a number of biologic systems to the extent that its gamma emitting radioactive isotope Rb^{86} (physical half-life 19.5 days) may be used as a tracer of potassium (3). Red blood cells, muscle, including heart muscle and most viscera exchange rubidium at about the same rate as potassium. More rubidium than potassium concentrates in liver, kidney, intestine, heart and spleen, and less in brain and bone (6). Less rubidium than potassium is excreted in the urine making rubidium undesirable as a means of determining total exchangeable potassium (10).

After it had been established that saliva could be used for the determination of total exchangeable potassium using K^{42} as a tracer, Rb^{86} was used in an attempt to study its applicability as a substitute for K^{42}. Doses of 250-300 microcuries Rb^{86} (specific activity 0.11-7.7 mc/mg) were administered orally to three patients. Total exchangeable potassium determinations had been done one week previously in this group of patients. The second group of two patients were given a single simultaneous mixed dose of 500 microcuries K^{42} and 200 microcuries Rb^{86}. Urine and saliva samples were collected as described above and were counted at daily intervals for three days until the radioactivity of K^{42} was no longer detectable. Total radioactivity less radioactivity after the third day was the K^{42} radioactivity (10).

RESULTS:

Tables 3 and 4 demonstrate the results of these studies.

DISCUSSION:

These data suggest that saliva may be used for the determination of exchangeable potassium using K^{42} and Rb^{86} as tracers. Exchange appears to be complete 24 hours after the administration of the tracer dose.

TABLE 3.

SPECIFIC ACTIVITIES AND K_e OF SALIVA USING RUBIDIUM 86

Case	Rb^{86} $\mu c/L$ / K^{39} Meq/L	S.A.	K_e Meq	Meq/Kg
1.	5.22 / 35.5	.147	2040	27.8
2.	4.43 / 21.5	.206	1456	29.4
3.	2.89 / 22.0	.131	2290	39.5
4.	2.34 / 21.0	.112	1720	26.2
5.	2.15 / 22.5	.096	2060	32.4

TABLE 4.

COMPARISON OF K_e VALUES USING K^{42} AND RB^{86}

Case	K_e Total Meq		
	K^{42}/Urine	K^{42}/Saliva	Rb^{86}/Saliva
1.	2210	2390	2040
2.	1520	1550	1456
3.	2210	2270	2290
4.	1860	1900	1720
5.	2260	2220	2060

Patients 1, 2 and 3 received K^{42} and Rb^{86} one week apart.
Patients 4 and 5 received K^{42} and Rb^{86} simultaneously.

In the earlier studies of body composition it was shown that potassium exchange is rapid in most viscera, fairly rapid in muscle, and slower in red blood cells, brain and bone. When three readily available sources of body potassium, red cells, plasma, and urine were studied, it was found that the red cell, the only easily sampled cellular compartment, could not be used for exchangeable potassium determinations because of slow exchange and short physical half-life (12.4 hours) of K^{42}. Plasma contains so little potassium and so little K^{42} following administration of permissible tracer doses that it, too, cannot be used. Urine, however, was found to mirror overall body exchange of potassium.

In vivo studies in rabbits and postmortem determinations in humans by Nadell showed that a large component of exchangeable potassium enters the gastrointestinal lumen (7). It is not clinically practical to obtain gastrointestinal secretions for examination. It does appear, however, that saliva, which is not only rich in potassium but also readily obtainable, may be used to advantage whenever urine cannot be obtained for examination.

Since approximately 10 per cent of the orally or intravenously administered tracer dose of K^{42} is excreted in the urine in 24 hours, this amount can safely be subtracted from the total amount administered in the calculation of K_e if there is urinary output. If the patient is anuric, a situation for which the salivary method here described would seem applicable, no correction for urinary loss would have to be made.

Rubidium has been shown to behave qualitatively similar to potassium in a number of biologic systems so that certain kaliokinetic phenomena can be studied by means of its radioactive isotope Rb^{86}.

Complete equilibrium of distribution between extracellular and intracellular compartments throughout the body is not established for several days. Burch

and his associates showed in control subjects and in a patient with congestive heart failure that equilibrium of distribution was not complete after eight days (3). Rubidium and cesium have been shown to enter skeletal muscle of rats in preference to potassium (8). Experiments in dogs showed that more Rb^{86} than K^{42} concentrated in liver, kidney, intestine, heart and spleen and less in brain and bone. In muscle and red blood cells both isotopes were present in equal proportions (6). It is apparent from these studies that Rb^{86} is not a satisfactory substitute for K^{42}. Nevertheless, our data indicate that Rb^{86} exchange in saliva is comparable to K^{42} 24 hours after its administration and that in saliva, at least, Rb^{86} can be used interchangeably with K^{42}. Its longer physical half-life makes prolonged observations possible.

SUMMARY:

1. Radioactive potassium (K^{42}) exchanges with its stable isotope (K^{39}) in the saliva within 24 hours after administration.

2. Radioactive rubidium (Rb^{86}) exchanges with K^{39} in the saliva at the same rate as does K^{42}.

3. These data suggest that saliva may be used in place of urine for the determination of total exchangeable potassium. This method might prove useful in clinical situations in which urine cannot be obtained or K^{42} is not readily available.

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Three Years Experience in the Therapeutic Use of Radioactive Gold Grains

Robert J. Dickson, M.D.
Baltimore

INTRODUCTION

In 1956, the procurement of radon seeds became more difficult because of the closure of several radon plants in our vicinity. An alternative method of implantation of radioactive materials was necessary and it was decided to purchase a gold grain gun. This was first described by Hodt, Sinclair and Smithers (1) from the Royal Marsden Hospital, London. The gun (Fig. 1) is a relatively simple instrument consisting of a handle, trigger, and loading mechanism to which is attached a needle. The magazine containing 15 gold grains is loaded into the needle which is then attached to the gun. The stilette is then pushed forward so that the grains are charged into the tip of the needle with the most distant grain at the tip. With each pull of the trigger, the stilette is advanced the length of one grain which is thus implanted into the tissue; the needle is withdrawn a specified distance and another grain is implanted. In this way a row of radioactive grains is implanted at a predetermined spacing through a single puncture wound.

Considerable difficulty was encountered in the supply of the radioactive material and initially the implement was used only sporadically. Later in 1957, radioactive gold grains became available from Atomic Energy of Canada, Ltd., through whom supplies have been obtained for the past two years. Because of the irradiation time necessary for the production of the required activity, the short half life of Au^{198}, and the distance involved, it was evident that considerable delay would be encountered if grains were ordered for a specific patient. It was therefore arranged that a regular supply of grains be delivered to the Department so that they would be immediately available for clinical use. The number to be implanted and the spacing required varied with their activity at the time of use. At the present time, two magazines, each containing 15 grains, are received weekly on Monday morning, the activity being calibrated so that on Wednesday at noon, each grain is equivalent to approximately 1 mc of radon or 4.8 mc of Au^{198}.

RADIOACTIVITY

The grains used with the gun are made of solid gold, coated with 0.2 mm platinum to filter all the Beta particles. Each grain is 2.5 mm long and 0.8 mm in diameter. The magazine is of pure aluminum and is activated, together with the contained grains, with a resultant activity on removal from the pile equiva-

lent to about that of 1 mc of Na^{24} ($T_{½} = 15$ hr). The magazine, therefore, requires careful handling. A special device is provided to hold the magazine while the screw ends are removed. The calculated exposure to the operator is 0.7r per hour at the trigger finger when 15 grains, each of 1 mc of radon equivalent are loaded in the normal length needle.

ECONOMY

The cost of the gun with four needles and the unloading device is approximately $300.00; that of the grains is $15.00 per magazine containing 15 activated grains. Each grain, therefore, costs $1.00 as against the $3.00 to $4.00 for each radon seed from most manufacturers. In addition, gold grains have the advantage that they may be re-activated if unused and a 50 per cent allowance is made for each full cartridge returned. The average cost of gold grains is therefore considerably less than that of radon.

RESULTS

During the three years since gold grains have become available, we have treated a total of 54 patients, the majority being during the past 18 months. They are grouped in Table 1. according to the anatomical site of their lesion.

In addition, radiation hypophysectomy has been attempted on twenty patients using gold grains of somewhat different structure and activity as will be described later.

Fig. 1. Royal Marsden Hospital Gold Grain Gun.

Head and Neck

Gold grains were used in two distinct ways, first as a palliative for recurrent or persistant disease following radium implant or external x-ray therapy, and secondly as a supplement to a radium implant. In situations where it would be difficult to place a radium needle accurately or where potential extension of disease had occured such as in the faucial pillars with a lesion in the lateral border of the tongue encroaching on the tonsillar fossa, it was felt that radioactive grains would be a satisfactory alternative to an inaccurately placed radium source. Figure 2 is an x-ray of an implant in the buccal mucosa with gold grains inserted both medially and laterally to the ascending ramus of the mandible. This patient had a localized lesion situated just anterior to the mandible and the posterior crossing radium needle would have been difficult to insert and would not have covered the potential spread of the disease on both sides of the bone. The specific sites of the head and neck lesions treated with gold grains are listed in Table 2.

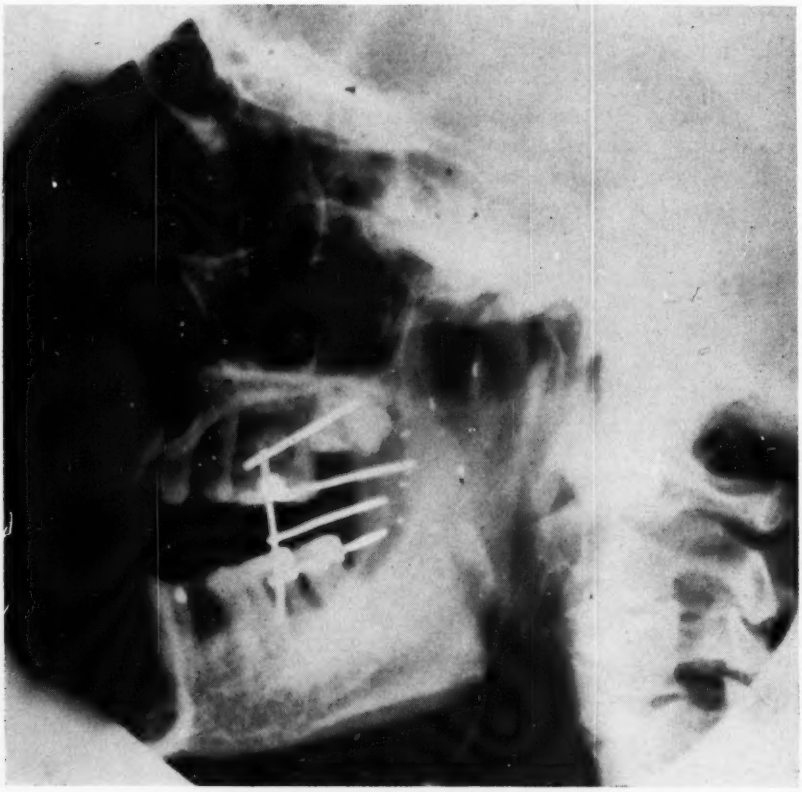

Fig. 2. Gold grains as supplement to radium in implant of buccal mucosa.

TABLE 1. ANATOMICAL SITES OF LESIONS OF PATIENTS TREATED BY IMPLANTATION OF RADIOACTIVE GOLD GRAINS

Site of Lesion	*No. Patients*
Head and neck	17
Breast	11
Genito-urinary	9
Metastatic nodes	8
Soft tissue and bone	2
Lung	2
Rectum	2
Bladder	1
Orbit	1
Brain	1
Total	54

Breast

The majority of the breast lesions treated were skin nodules in or near previously irradiated skin. Very satisfactory regression of nodules was achieved. Figure 3 is of one such patient prior to treatment. This woman had had a radical mastectomy with skin grafting of the area and post-operative X-ray therapy. During the five years that she has been under observation in our hospital she has had innumerable skin lesions treated by local superficial therapy but these current areas were so close to the very thin graft that the risk of breakdown was considerable. Gold grains were inserted into the active edge of these and other nodules with the result illustrated in Fig. 4.

Genito-urinary

Implants into recurrent nodules in the vagina, recto-vaginal septum and pelvic nodes were made per vaginam. Some patients received gold grain implants at laparotomy when unexpected pelvic nodules were discovered. One great advantage of receiving the grains on a routine order is that they are available in such circumstances. Similarly, one carcinoma of the bladder was treated by gold grain implantation instead of a segmental resection as planned because the lesion was found to be surgically irremovable.

Metastatic Nodes

Nodes from head and neck lesions, breast carcinoma, and inguinal adenopathy from carcinoma of the vulva were treated. However if the nodes were large it was not considered wise to use such a localized method of therapy.

Soft tissue and Bone

One reticulum cell sarcoma and one Ewing's Tumor of the fibula with extension into the soft tissues were implanted, both with favorable local results.

TABLE 2. SPECIFIC SITES OF HEAD AND NECK LESIONS TREATED WITH RADIOACTIVE GOLD GRAINS

Site of Lesion	*No. Patients*
Tongue	9
Floor of mouth	2
Tonsil	2
Buccal mucosa	1
Palate	1
Epiglottis	1
Pyriform sinus	1
Total	17

Lung

It was originally felt that with the immediate availability of gold grains, lung tumors found at thoracotomy to be irremovable could be implanted, thus delivering some radiation to the periphery of the lesion and also giving an accurate radiological localization of the area requiring treatment when external X-ray therapy was to be used (Fig. 5). In the first case the localization was undoubtedly most advantageous in beam direction. The other patient unfortunately succumbed to the operation and it was the feeling of the surgeon that the implanting needle had contributed to his demise. The needle then in use was 2 mm in diameter and it might have been easy to perforate a large vessel. The diameter of the needles has now been reduced to 1.25 mm which should reduce the risk of perforation.

Rectum

Two patients with ulcerating skin extension from carcinoma of the rectum received gold grain implants with satisfactory local response.

Orbit

The one case in this category was that of a young boy with recurrent rhabdomyosarcoma following enucleation. A combination of external radiation and gold grain implant has been followed by a two year period of freedom from disease (Fig. 6).

Brain

A recurrent glioma of the mid brain was implanted through the burrholes using an image intensifier for direct visualization of the path of the needle. The area was very accurately delineated by ventriculography and there was no difficulty in placing the grains in the desired position. No ill effects from this procedure were noted immediately but the response cannot yet be evaluated be cause of the short period of observation since the procedure.

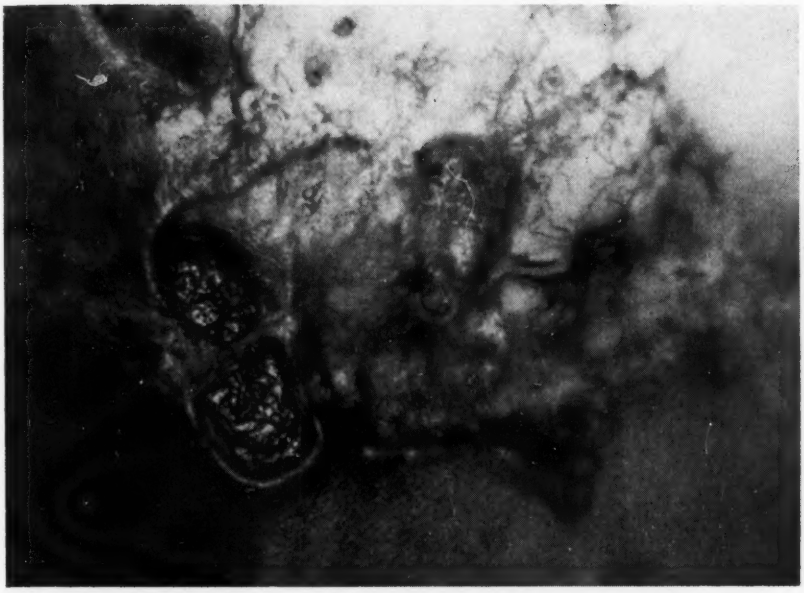

Fig. 3. Skin nodules from carcinoma of the breast before treatment.

Fig. 4. Skin nodules after gold grain implant.

Hypophysectomy

In addition to the use of the gold grain gun, we have attempted radiation hypophysectomy with solid gold grains implanted trans-sphenoidally. These grains have no platinum coating and are of activity up to 35 mc each to produce maximal local destruction by Beta radiation. The results of this procedure are in the process of evaluation.

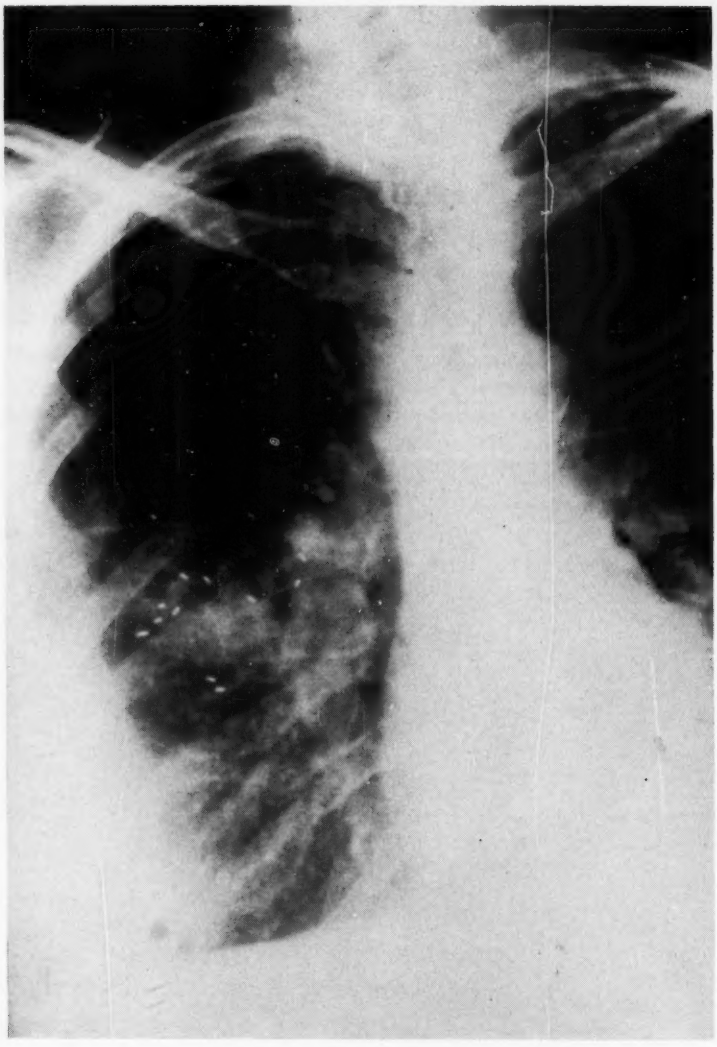

Fig. 5. Gold grains inserted around a lung tumor found at thoractomy to be inoperable.

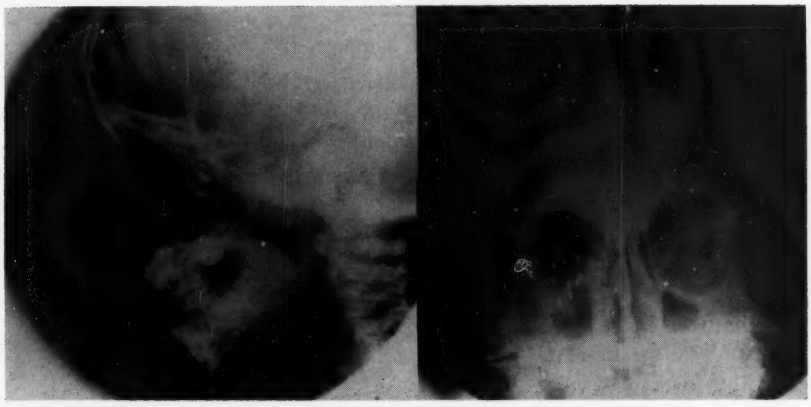

Fig. 6a. Implant into recurrent Rhabdomyosarcoma of orbit.
Fig. 6b. Implant into recurrent Rhabdomyosarcoma of orbit.

SUMMARY

1. The Royal Marsden Hospital gold grain gun has been found to be a very satisfactory alternative to the implantation of radon seeds.

2. Relative to radon, the cost of gold is very much less.

3. The versatility of the instrument is demonstrated by the large variety of lesions which have been treated. Excellent palliation, comparable to that with radon seeds, was obtained in most of the cases where such was the intent. Response of up to two years continues in several patients treated with the hope of cure. The long-term effects of this treatment cannot be evaluated at this time.

4. The immediate availability of gold grains received on a regular basis is very useful when a radioactive implant is required unexpectedly during an operative procedure.

5. One possible disadvantage of the gold grain gun is that the large bore of the needle and the rigidity of the applicator could theoretically perforate a major blood vessel, but this risk is reduced with the smaller needle now in use.

REFERENCE

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Society of Nuclear Medicine

Eighth Annual Meeting

Call for Papers and Scientific Exhibits

Last Call by Program Committee for Abstracts and Exhibits

Members are hereby asked to aid in the preliminary planning of the program. They may do so by submitting a title of a paper or exhibit, by suggesting a paper by some other member (or non-member), or by indicating preferences for such procedures as (a) single sessions, (b) sessions by topical arrangement, (c) instructional sessions, (d) symposia, etc. The deadline for titles, abstracts and suggestions is February 15, 1961. These should be sent to the Program Chairman:

Dr. Richard E. Peterson
Veterans Administration Hospital
Iowa City, Iowa

Instructions for Abstracts

Abstracts should be a verbatim copy, not exceeding 250 words, double-spaced on 8½ × 11″ regular typewriter paper with five carbon copies, for review of program chairman and his committee.

Non-members may be invited to submit abstracts by active members. Non-member authors should be indicated by an asterisk (*) following their name. If none of the authors is a member, the name of the sponsoring member should be given.

Titles should be brief, with capitalization of the entire title. Authors' names should be underlined and followed by one degree and current title. Authors' institution should be identified in parenthesis.

Example: THE USE OF RADIOISOTOPES IN NUCLEAR MEDICINE. *John H. Doe, M.D., Chief of Laboratory and William R. Doe, Ph.D.,* Physicist,* (the Fermi Institute of Nuclear Medicine)

In consideration of each abstract, the program committee will either accept the abstract for oral presentation, or suggest its presentation as an exhibit, or demonstration, or designate it to be read by title, or to reject it as unsuitable. Abstracts of all papers accepted (including those read by title only) will be published. Essayists will be expected to submit a complete manuscript before the Annual Meeting for consideration by the Editorial Board of the *Journal of Nuclear Medicine.*

Instructions for Scientific Exhibits

For those submitting scientific exhibits, please add the following information: the amount of space required (not to exceed 6 feet in depth, 8 feet in height and 8 feet in width); whether or not special equipment, aside from one regular electrical outlet, will be required and whether tables and/or chairs are required. Exhibit titles and other pertinent data should be mailed on or before December 1st, 1960, to:

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Dinner meeting of the Board of Trustees

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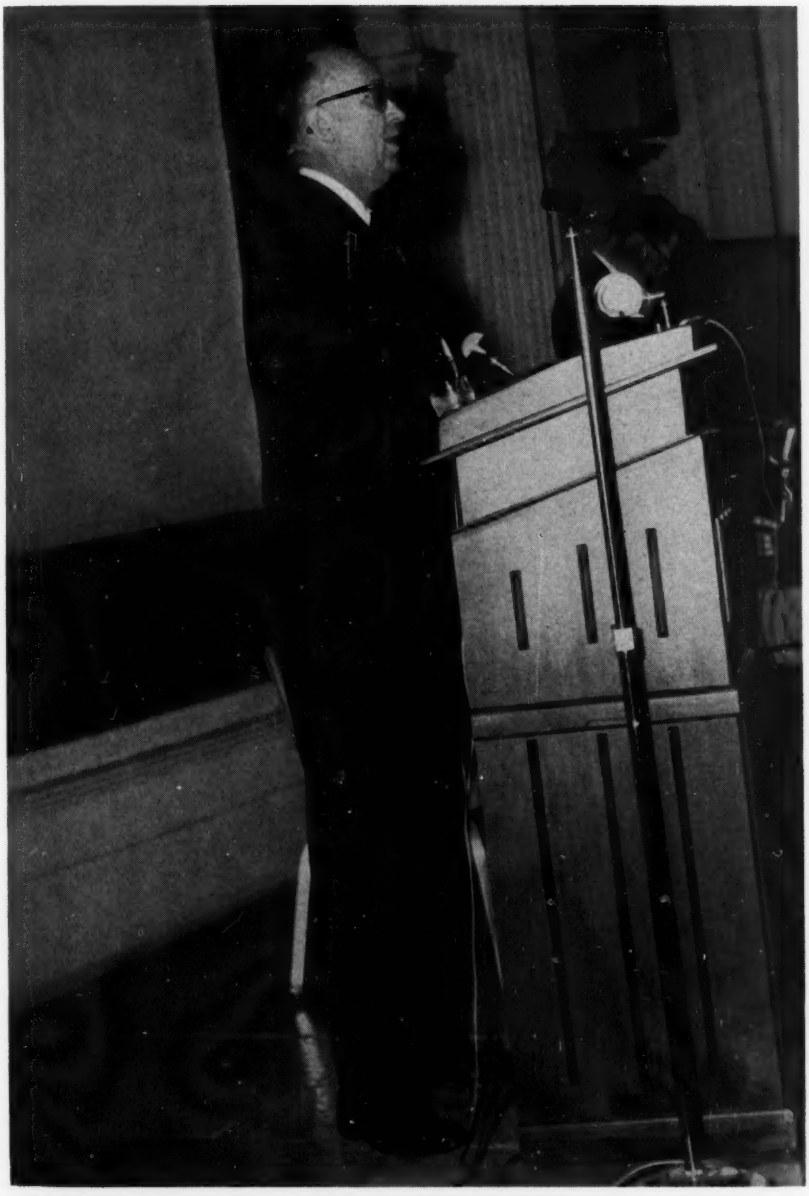
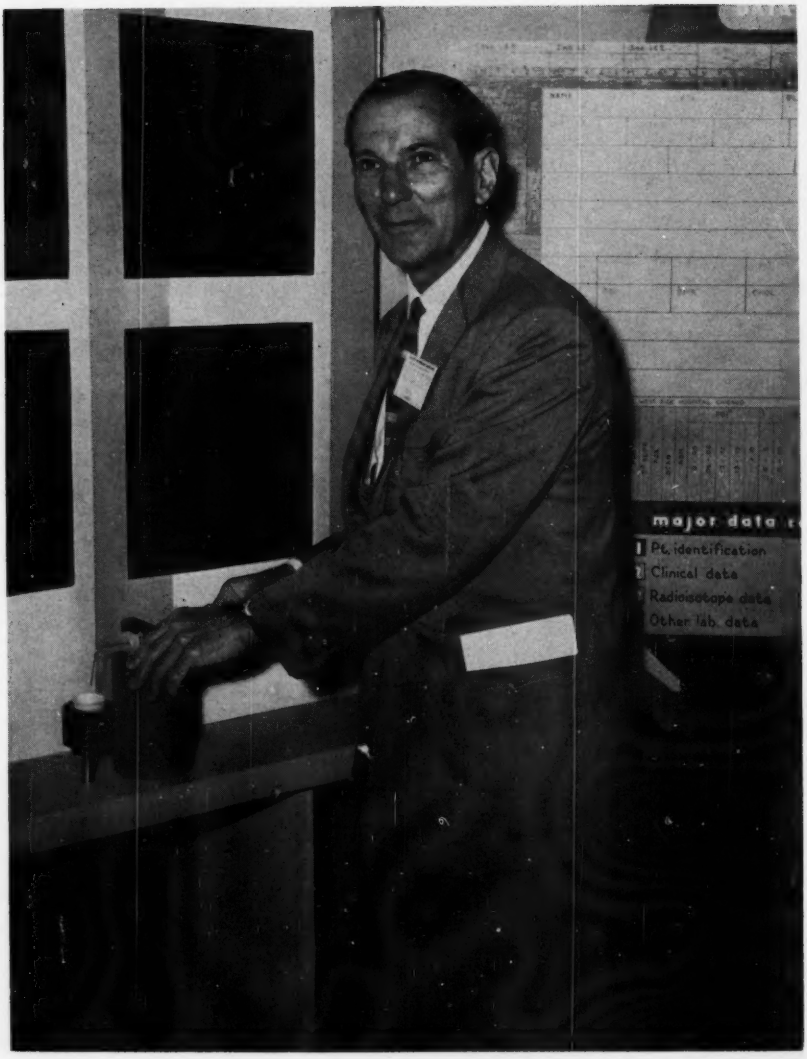


Dr. John H. Lawrence, Honorary Member of the Society of Nuclear Medicine, providing introductory remarks for the Ernest O. Lawrence Memorial Lecture at the Seventh Annual Meeting.



Dr. Paul C. Aebersold, Honorary Member of the Society of Nuclear Medicine and Director of the Office of Isotopes Development for the A.E.C., visiting the scientific and technical exhibit area.

Past Presidents of the Society at Estes Park, Colorado. l. to r.: Asa Seeds, M.D., Vancouver, Washington; Norman J. Holter, M.S., Helena, Montana; Marshall Brucer, M.D., Oak Ridge; Henry L. Jaffe, M.D., Los Angeles; Henry H. Turner, M.D., Oklahoma City.

Dr. J. R. Maxfield, Jr., Program Chairman for the Society's Seventh Annual Meeting and Dr. Herbert Vetter, Head, Section of Medicine, Dep't. of Research and Isotopes, International Atomic Energy Agency, Vienna, Austria.

Dr. Edward Teller presenting the First Annual Lecture Series in honor of Dr. Ernest O. Lawrence at the Seventh Annual Meeting of the Society in Estes Park, Colorado, June 24, 1960.